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(71) Applicant *(for all designated States except US)*: **SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.** [IT/IT]; Viale Shakespeare, 47, I-00144 Roma (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GIANNESSI, Fabio** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). **TASSONI, Emanuela** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km 30,400, I-00040 Pomezia (IT). **DELL'UOMO, Natalina** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km 30,400, I-00040 Pomezia (IT). **BRUNETTI, Tiziana** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). **TINTI, Maria, Ornella** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, km 30,400, I-00040 Pomezia (IT). **ARDUINI, Arduino** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p., A., Via Pontina, Km.30,400, I-00040 Pomezia (IT). **PESSOTTO, Pompeo** [IT/IT]; c/o Sigma-Tau Industrie Faramceutiche Riunite S.p., A., Via Pontina, Km. 30, 400, I-00040 Pomezia (IT).

(74) Agents: **SPADARO, Marco** et al.; Cavattoni- Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).

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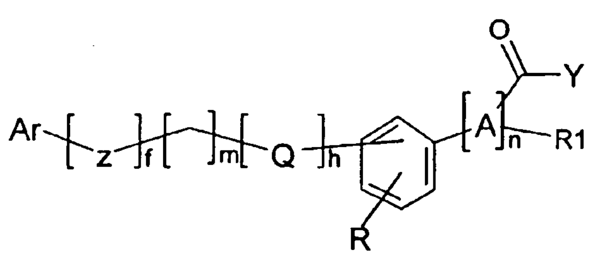
(54) **Title:** PHENY(ALKYL)CARBOXYLIC ACID DERIVATIVES AND DIONIC PHENYLALKYLHETEROCYCLIC DERIVATIVES AND THEIR USE AS MEDICINES WITH SERUM GLUCOSE AND/OR SERUM LIPID LOWERING ACTIVITY



(I)

(57) **Abstract:** Formula (I) compounds are described: Where the groups are as defined here below, and their use as medinies, particularly as serum glucose and serum lipid lowering agents. Said medicines are useful for the prophylaxis and treatment of diabetes, particularly type 2, and its complications, Syndrome X, the various forms of insulin resistance, and hyperlipidaemias, and present reduced side effects, and, particularly, reduced or no liver toxicity.

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Phenyl(alkyl)carboxylic acid derivatives and dionic phenylalkylheterocyclic derivatives and their use as medicines with serum glucose and/or serum lipid lowering activity.

The invention described herein relates to phenyl(alkyl)carboxylic acid derivatives and dionic phenylalkylheterocyclic derivatives and to their use as medicines, particularly with serum glucose and/or serum lipid lowering activity.

Background to the invention

Diabetes is a widespread disease throughout the world and is associated with major clinical complications including macrovascular (atherosclerosis) and microvascular (retinopathy, nephropathy and neuropathy) damage. Such complications are inevitable consequences of the disease and constitute a serious threat to the subject's life and well-being. Diabetes is associated with various abnormalities such as obesity, hypertension and hyperlipidaemia. Various clinical forms of diabetic disease are known, the most common being type 2 and type 1 diabetes. Type 2 diabetes is characterised by reduced sensitivity to the action of insulin (insulin resistance) and gives rise to an increase in actual insulin levels in the body in an attempt to compensate for this deficiency and to a consequent increase in glucose levels. Numerous reports have confirmed the involvement of insulin resistance in many disease conditions in addition to type 2 diabetes itself, such as

dyslipidaemia, obesity, arterial hypertension and certain macro-vascular and microvascular manifestations characteristic of diabetes. The combination of insulin resistance and obesity, hypertension and dyslipidaemia is known as Syndrome X.

Drugs used for many years such as the biguanidines and sulphonylurea drugs are available on the market for the treatment of type 2 diabetes. In the case of the biguanidines (the best known of which is metformin) the mechanism of action is still unclear and the efficacy would not appear to afford satisfactory cover throughout all the hours of the night. Sulphonylurea drugs promote the secretion of insulin by the β-cells and may present episodes of hypoglycaemia as a possible side effect.

Drugs recently introduced onto the market are the thiazolidinediones, i.e. insulin-sensitising antidiabetic compounds such as troglitazone (*J. Med. Chem.*, **1989**, *32*, 421-428), pioglitazone (*Arzneim. Forsch./ Drug Res.*, **1990**, *40 (1)*, 37-42), and rosiglitazone (*Bioorg. Med. Chem. Lett.*, **1994**, 4, 1181-1184) which are capable of reducing hyperglycaemia, diabetic hyperlipidaemia and insulin levels. These compounds are high-affinity synthetic ligands of PPARγ (*J. Biol. Chem.*, **1995**, *270*, 12953-12956).

Peroxisome proliferator activated receptors (PPARs) are receptors belonging to the superfamily of nuclear receptors whose function is to control the expression of genes involved in carbohydrate and lipid metabolism (*J. Med. Chem.*, **2000**, *43*, 527-

550). Various subtypes of PPARs have been identified: PPARγ, PPARα and PPARβ (also known as PPAR δ). The gamma isoform (PPARγ) is involved in the regulation of the differentiation of adipocyles and in energy homeostasis, whereas the alpha isoform (PPARα) controls fatty acid oxidation resulting in modulation of the levels of free fatty acids in plasma. In structure-activity relationship studies aimed at identifying new molecules endowed with potential antidiabetic action, a correspondence has been confirmed between PPARγ activation and serum glucose lowering activity (*J. Med. Chem.*, **1996,** *39*, 665-668; *J. Med. Chem.*, **1998,** *41*, 5020-5036; 5037-5054; 5055-5069). The insulin-sensitising action would appear to be related, as far as this first series of compounds is concerned, to the fatty acid recruitment action regulated by activated PPARγ which is thought to lead to an improvement in the insulin resistance of the tissues, enhancing serum glucose levels and lowering insulin levels. (*Diabetes*, **1998,** *47*, 507-514).

The side effects already observed with troglitazone and feared also in the case of the other compounds of this class are:: severe liver toxicity (which caused the withdrawal of troglitazione from the US market), increased cholesterol, weight gain and oedema.

In recent years molecules with a mixed profile, i.e. ligands of PPARγ and PPARα, have emerged (KRP 297, *Diabetes*, **1998**, *47*, 1841-1847; DRF 2725, *Diabetes*, **2001**, *50*, suppl.2, A108; AZ 242, *Diabetes*, **2001**, *50*, suppl. 2, A121-A122). These compounds are

potentially capable of exerting a good measure of control of diabetic disease, while presenting a serum glucose and serum lipid lowering action with fewer side effects typical of the first series of compounds in the thiazolidinedione class, consisting exclusively of PPARγ ligands.

Not all the scientific community, however, agrees with this line of thinking. Recent studies on new-generation compounds, whether thiazolidinedione derivatives or otherwise (MC555, *J. Biol. Chem.*, **1998**, *Vol. 273 (49)*, 32679-32684; NC2100 *Diabetes*, **2000**, *49*, 759-767, YM440, *Metabolism*, **2000**, *49*, 411-417), in gene transactivation tests, *in-vitro* glucose uptake experiments with muscle tissue and *in-vivo* experiments in transgenic animals with deficient PPARγ expression, have led to the hypothesis that there is no direct relationship between PPARγ activation and the serum glucose and serum lipid lowering activity of these compounds (*Toxicology Letters*, **2001**, *120*, 9-19). This may indicate that the serum glucose lowering activity of these molecules is not necessarily related to PPARγ activation and that these compounds may be capable of modulating carbohydrate and lipid metabolism through interaction with other biochemical targets. This is confirmed by the work of investigators who have opted for the use of *in-vivo* screening in diabetic animals (db/db mice, ob/ob mice) and for *in-vitro/in–vivo* tests (L6 cells), (*J. Med. Chem.*, **1998**, *41*, 4556-4566) in order to identify possible insulin-sensitising agents which are not necessarily

good PPAR ligands. These experiments have led to the selection of compounds still being investigated with promising antidiabetic activity in animal models (DRF 2189, *J. Med. Chem.*, **1998**, *41*, 1619-1630; JTT-501, *J. Med. Chem.*, **1998**, *41*, 1927-1933).

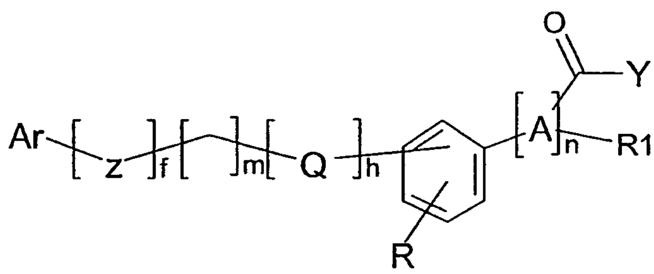
In conclusion, then, since the first compounds belonging to the thiazolidinedione class have proved to be associated with substantial hepatotoxic and other side effects, probably related to their PPARγ activity, the scientific community would now appear to be oriented towards the search for new compounds with a different mechanism of action which induce a similar or better effect on insulin sensitivity and glucose homeostasis without toxic side effects (*J. Med. Chem.*, **2001**, *44*, 2601-2611).

Summary of the invention

It has now been found that compounds with formula (I) have been reported as being active as serum glucose and serum lipid lowering agents and are endowed with low toxicity and are therefore useful as medicines, particularly for the treatment of hyperlipidaemias and hyperglycaemias.

The preferred applications are the prophylaxis and treatment of diabetes, particularly type 2 and its complications, Syndrome X, the various forms of insulin resistance and hyperlipidaemias.

The object of the invention described herein are formula (I) compounds:



I

where:

A is CH; alkanylilidene with 2 to 4 carbon atoms, particularly CH_2-CH; alkenylilidene with 2 to 4 carbon atoms, particularly CH=C;

Ar is monocyclic, bicyclic or tricyclic C_6-C_{10} aryl or heteroaryl, containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, possibly substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen; monocyclic, bicyclic or tricyclic arylalkyl or heteroarylalkyl containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, where the alkyl residue contains from 1 to 3 carbon atoms, said arylalkyl or heteroarylalkyl possibly substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen;

f is the number 0 or 1;

h is the number 0 or 1;

m is a whole number from 0 to 3;

n is the number 0 or 1 and if n is 0, R_1 is absent, and COY is directly bound to benzene);

Q and Z, which may be the same or different, are selected from the group consisting of NH, O, S, NHC(O)O, NHC(O)NH, NHC(O)S, OC(O)NH, S(CO)NH, C(O)NH, and NHC(O);

R is selected from R_2, OR_2;

R_1 is selected from H, COW, SO_3^-, OR_3, =O, CN, NH_2, NHCO(C_6-C_{10})Ar, where Ar may possibly be substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen;

R_2 is selected from H, straight or branched C_1-C_4 alkyl, possibly substituted by at least one halogen;

R_3 is selected from H, straight or branched C_1-C_4 alkyl, possibly substituted by at least one halogen, (C_6-C_{10})$ArCH_2$, where Ar is possibly substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen;

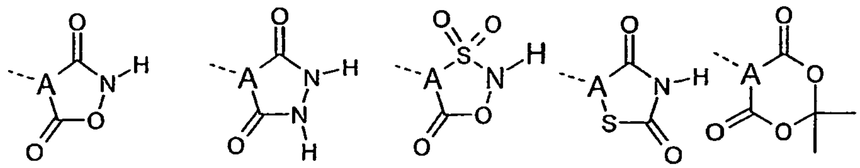
W is selected from OH, OR_4, NH_2;

R_4 is straight or branched C_1-C_4 alkyl;

Y is selected from OH, OR_5, NH_2;

R_5 is straight or branched C_1-C_4 alkyl;

or A, COY and R_1 together form a cycle of the type:



their pharmacologically acceptable salts, racemic mixtures, individual enantiomers, geometric isomers or stereoisomers, and tautomers.

A further object of the invention described herein is the use of said compounds as medicines for the treatment of hyperlipdaemias and hyperglycaemias, particularly for the treatment of type 2 diabetes and its complications, as well as pharmaceutical compositions containing said compounds as active ingredients.

These and other objects will be described in detail, also with the aid of examples.

Detailed description of the invention

In the formula (I) compounds, what is meant by alkanylilidene with 2 to 4 carbon atoms are the groups $-(CR_6R_7)_p-CR_8<$, where R_6, R_7 and R_8 are hydrogen, methyl or ethyl, and p is a whole number from 1 to 3. What is meant by alkenylilidene with 2 to 4 carbon atoms are the groups $-CR_9R_{10}=C<$, $-CR_9R_{10}-CR_{11}=C<$, $-CR_9=CR_{10}-CR_{11}<$, -CH2-CH2-CH=C< -CH=CH-CH2-CH<, -CH=CH-CH=C<, -CH2-CH=CH-CH<, -CH=C=CH-CH<, -CH2-CH=C=C<, where R_9, R_{10}

and R_{11} are hydrogen, methyl or ethyl. In all cases the symbol < identifies the bond of A with COY and R_1.

In the formula (I) compounds, a first group of preferred compounds consists of compounds in which Ar is a heteroaryl, preferably containing nitrogen as the heteroatom, e.g. indole, or pyridine, bound to the rest of the molecule via all the positions allowed; particularly preferred among these are the 1-indolyl and 1-pyridyl groups. In the context of this first group, preferably f is 0, m is 1 or 2, Q is oxygen, and R is hydrogen.

A second group of preferred compounds consists of compounds in which Ar is an aryl, possibly substituted by one or more atoms of halogen, alkyl, alkoxy or lower haloalkyl, preferably methyl, methoxy or trifluoromethyl, nitro, mono- or di-alkylamine. In the context of this second group, preferably f is 0, m is 0, 1 or 2, Q is oxygen or HNC(O)O, and R is hydrogen.

Particularly preferred are the compounds where R_1 is COW.

Even more preferred are the following compounds:

i. Diethyl 4-[2-(1-indolyl)ethoxy]benzylidenemalonate

ii. Diethyl 4-[2-(1-indolyl)ethoxy]benzylmalonate

iii. Dimethyl 4-[2-(1-indolyl)ethoxy]benzylidenemalonate

iv. Dimethyl 4-[2-(1-indolyl)ethoxy]benzylmalonate

v. 4-[2-(1-indolyl)ethoxy]benzylmalonic acid

vi. Methyl (2S)-amino-2-[4-[2-(1-indolyl)ethoxy]phenyl]-acetate

vii. Methyl 4-[2-(1-indolyl)ethoxy]benzoate

viii. Methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]propanoate

ix. Methyl 2-[4-[2-(1-indolyl)ethoxy]phenyl]acetate

x. Methyl 2-sulpho-2-[4-[2-(1-indolyl)ethoxy]phenyl]acetate sodium salt

xi. Methyl (S)-2-benzoylamino-2-[4-[2-(1-indolyl)ethoxy]-phenyl]acetate

xii. Methyl 2-hydroxy-3-[4-[2-(1-indolyl)ethoxy]phenyl]-propanoate

xiii. Dimethyl 4-[2-[4-(dimethylamino)phenyl]ethoxy]benzylmalonate

xiv. Methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyano-propenoate

xv. Methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyano-propanoate

xvi. Dimethyl 4-[2-(3-indolyl)ethoxy]benzylidenemalonate

xvii. Dimethyl 4-[2-(1-naphthyl)ethoxy]benzylmalonate

xviii. Dimethyl 4-[2-(2-pyridyl)ethoxy]benzylmalonate

xix. Dimethyl 4-[2-(4-chlorophenyl)ethoxy]benzylmalonate

xx. 5-[4-[2-(4-chlorophenyl)ethoxy]phenylmethylene]-thiazolidine-2,4-dione

xxi. 5-[4-[2-(4-chlorophenyl)ethoxy]phenylmethyl]thiazolidine-2,4-dione

xxii. Dimethyl 3-[2-(4-chlorophenyl)ethoxy]benzylmalonate

xxiii. Dimethyl 3-[2-(phenyl)ethoxy]benzylmalonate

xxiv. Dimethyl 3-[N-(4-trifluoromethylbenzyl)carbamoyl]-4-methoxybenzylmalonate

xxv. Dimethyl 4-methoxy-3-[2-(4-chlorophenyl)ethoxy]benzylmalonate

xxvi. Dimethyl 3-(2-phenylethoxy)-4-methoxy benzylmalonate

xxvii. Dimethyl 4-[2-(4-methoxyphenyl)ethoxy]benzylmalonate

xxviii. Dimethyl 4-[3-(4-methoxyphenyl)propyloxy]benzyl-malonate

xxix. Dimethyl 4-[2-(2-naphthyl)ethoxy]benzylmalonate

xxx. (2S)-2-benzoylamino-3-[4-[(4-methoxybenzyl)-carbamoyl]oxyphenyl]ethyl propanoate

xxxi. Dimethyl 4-[[(4-methoxybenzyl)carbamoyl]oxy]benzyl-malonate

xxxii. Dimethyl 4-[[(4-trifluorotolyl)carbamoyl]oxy]benzyl-malonate

xxxiii. Dimethyl 4-[[(2,4-dichlorophenyl)carbamoyl]oxy]benzyl-malonate

xxxiv. Dimethyl 4-[[(4-chlorophenyl)carbamoyl]oxy]benzyl-malonate

xxxv. Dimethyl 4-[2-(pyridinio)ethoxy]benzylmalonate methane-sulphonate

xxxvi. Dimethyl 4-[[(4-nitrophenyl)carbamoyl]oxy]benzyl-malonate

xxxvii. Dimethyl 3-[[(4-methoxybenzyl)carbamoyl]oxy]benzyl-malonate

xxxviii. Dimethyl 3-[[(4-butylphenyl)carbamoyl]oxy]benzyl-malonate

xxxix. Dimethyl 4-[[(4-butylphenyl)carbamoyl]oxy]benzyl-malonate

xl. Dimethyl 3-[[(4-chlorophenyl)carbamoyl]oxy]benzyl-malonate

xli. (Z)-2-ethoxy-3-[4-[2-(4-chlorophenyl)ethoxy]phenyl]ethyl propenoate

xlii. (E)-2-ethoxy-3-[4-[2-(4-chloro-phenyl)ethoxy]-phenyl]ethyl propenoate

xliii. (R,S)-2-ethoxy-3-[4-[2-(phenyl)ethoxy]phenyl]ethyl propanoate

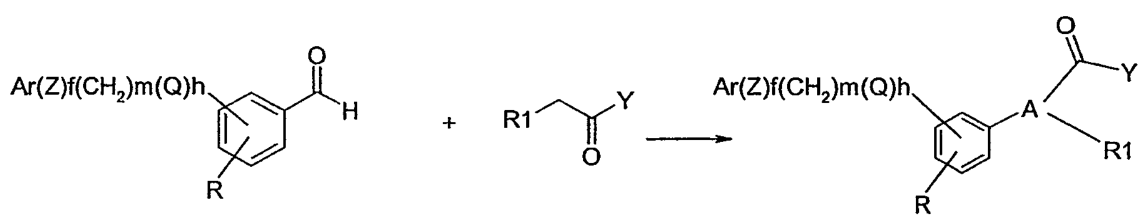
xliv. (R,S)-2-ethoxy-3-[4-[2-(4-chloro-phenyl)ethoxy]-phenyl]methyl propanoate

xlv. Dimethyl 4-[2-(2,3-dimethyl-1-indolyl)ethoxy]benzyl-malonate

The formula compounds are prepared using the reactions described in methods A-H.

In the case of formula (I) compounds in which A is akenylilidene, R_1 = COW, CN and Y = OH, OR_5, NH_2, or R_1 together with COY and A forms a cycle as indicated in formula (I) above, method A described here below can be used, as exemplified by A = -CH=C<.

Method A:



Ia Ib I

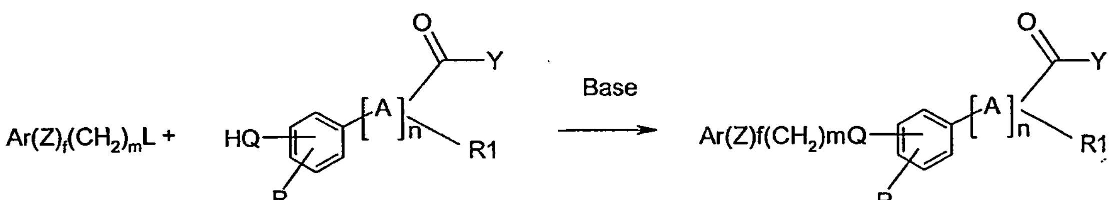
Unles otherwise specified, the meanings of the various symbols are intended to coincide with those indicated in the general formula.

The compounds of general formula I can be synthesised according to the diagram described above starting from compounds of general formula Ia and formula Ib in aprotic solvents such as toluene, refluxed with Dean-Stark, for time periods ranging from 5 to 24 hours, preferably 18 hours, in the presence, as a catalyst, of a salt of an organic base with an organic acid, such as piperidine

acetate, normally used in Knovenagel reactions, or in aprotic dipolar solvents such as DMF (*Synthetic Communications*, **2000**, *30 (4), 713-726*), possibly in the presence of an organic base such as piperidine, at a temperature ranging from 20 to 100°C, preferably 80°C, for reaction times ranging from 1 hour to 3 days, preferably 2 days.

In the case of formula (I) compounds in which Q is selected from NH, O, S, NHC(O)S, and NHC(O)O, method B described here below can be used.

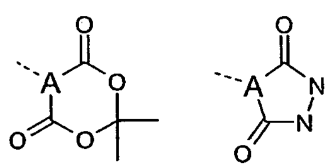
Method B:



Ic Id I

where L is an exit group such as MsO, TsO, Br, Cl, I

A, COY e R1 possono formare un ciclo =



A, Coy and R1 may form a cycle =

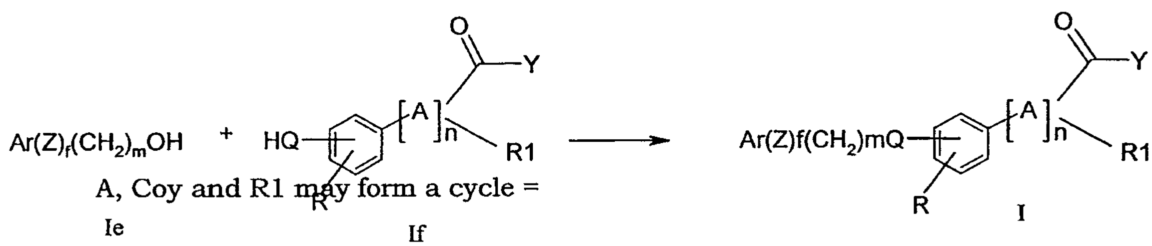
Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in formula (I) above.

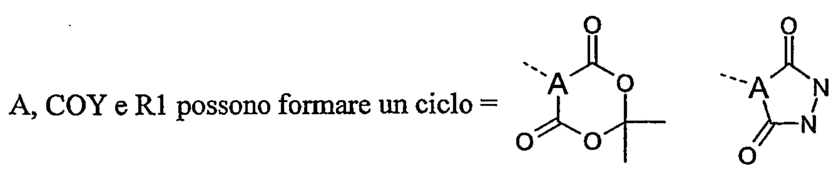
The general formula I compounds can be synthesised according to the diagram described above starting from compounds of general formula Ic, Id, where L is an exit group, such as, for

example, halogen, p-toluenesulphonate and methanesulphonate. The reaction is conducted in aprotic solvents such as DMF, DMSO and THF, in the presence of a base such as K_2CO_3 or KOH, or hydrides of alkaline metals such as NaH, possibly in an inert atmosphere which can be maintained using gases such as N_2 and Ar. The reaction temperature can range from 0 to 120°C, preferably 30-100°C, and the reaction times from 1 to 48 hours, preferably 6 to 18 hours.

In the case of formula (I) compounds in which Q is selected from O, or S, method C described here below can be used.

Method C:





Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in formula (I) above.

The general formula I compounds can be synthesised according to the diagram described above starting from compounds

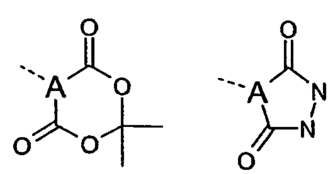
of general formula Ie, If, using as condensing agents triarylphosphine/dialkylazodicarboxylic esters such as PPH_3/DEAD and similar compounds that can be used in a ratio of 1 to 2 equivalents to the substrates, preferably 1.3-1.5 equivalents. The reaction can be conducted in aprotic solvents such as THF, DME, $CHCl_3$ and the like, possibly in an inert atmosphere that can be maintained using gases such as N_2 and Ar. The reaction temperature can range from 0 to 60°C, preferably 20 to 40°C, and the reaction time from 3 hours to 6 days, preferably 18 hours to 3 days.

In the case of formula (I) compounds in which Q is selected from NHC(O)O, NHC(O)NH, NHC(O)S, OC(O)NH, or SC(O)NH, method D described here below can be used.

Method D:

Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in formula (I) above, and X is -NCO when M is selected from OH, NH_2, SH, or X is OH, SH, NH_2 when M is NCO.

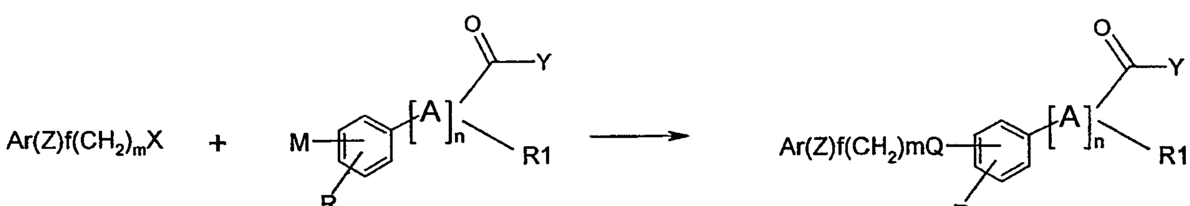
A, Coy and R1 may form a cycle =

A, COY e R1 possono formare un ciclo = 

The general formula (I) compounds can be synthesised according to the diagram described above starting from compounds of general formula Ig, Ih, if M or X is an NCO group, in aprotic solvents such as CH_3CN, THF, $CHCl_3$ and the like, possibly in the presence, as a catalyst, of an organic base such as triethylamine, possibly in an inert atmosphere maintained with gases such as N_2 and Ar. The reaction temperature can range from 0 to 40°C, preferably 25°C, and the reaction time from 1 to 48 hours, preferably 18 hours.

In the case of formula (I) compounds in which Q is selected from NHC(O) or C(O)NH, method E described here below can be used.

Method E:



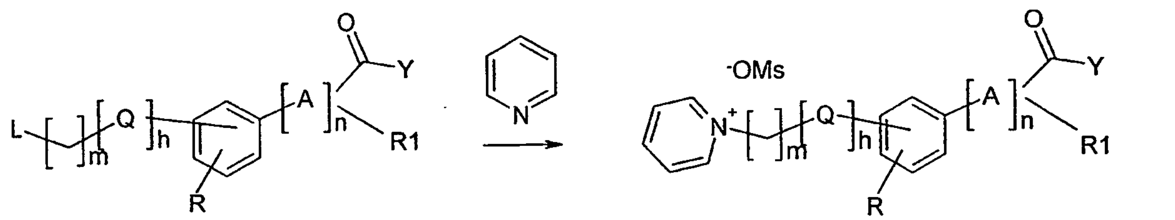
Ii Il I

Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in formula (I) above, and X is COOH when M is NH_2, and X is NH_2 when M is COOH.

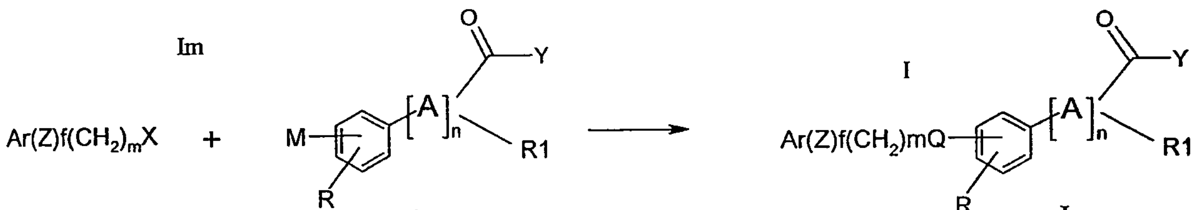
The general formula (I) compounds can be synthesised according to the diagram described above starting from compounds of general formula Ii, Il when X or M is a COOH group, using condensing agents such as diethylphosphorocyanidate, EEDQ, DCC oo CDI and the like, in a ratio of 1-3 equivalents to the substrates, preferably 1-1.5 equivalents, conducting the reaction in organic solvents such as DMF, CH_3CN, $CHCl_3$, THF and the like, at a temperature ranging from 20 to 80°C, preferably 25°C, for reaction times ranging from 18 hours to 3 days, preferably 24 hours. The synthesis can also be conducted by derivatising the acid as acid halogenide and then effecting the condensation in the presence of a proton acceptor such as triethylamine, in conditions similar to those described above.

In the case of formula (I) compounds in which Ar is an aromatic heterocycle, method F described here below can be used, as exemplified by the pyridinium group.

Method F



Im I



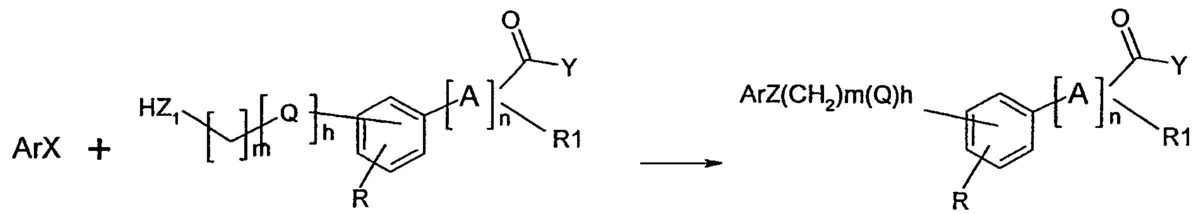
Ii II I

Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in formula (I) above, and L is an exit group such as MsO, TsO, Br, Cl, or I; m is a whole number from 1 to 3.

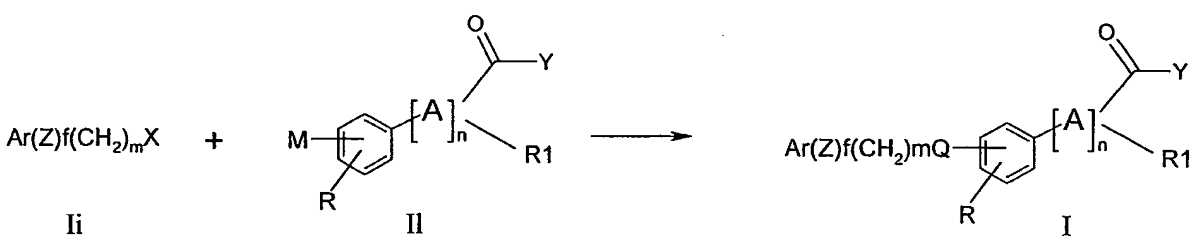
The general formula (I) compounds can be synthesised starting from compounds of general formula Im according to the diagram described above, where L is an exit group such as, for example, halogen, p-toluenesulphonate and methanesulphonate. The reaction is conducted using the same conditions as described in method B.

In the case of formula (I) compounds in which Z takes on the meanings described in the general formula with the exclusion of NH, method G described here below can be used.

Method G:



In Ip I

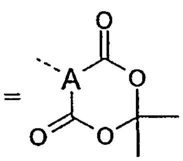
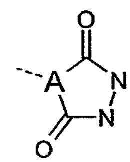


Ii Il I

Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in formula (I) above, and X is selected from NCO, COOH, OC(O)Cl, SC(O)Cl when Z_1 is selected from O, S, NH, or X is selected from OH, SH when Z_1 is O, or X is NH_2 when Z_1 is COOH.

The general formula (I) compounds can be synthesised starting from compounds of general formula In, Ip according to the diagram described above, when X or Z1 is a COOH group, and X or Z_1 is an O or N group, using the reaction conditions described in method E. When X is an NCO group and Z_1 is an O, N or S group, the reaction can be conducted in the conditions described in method D*. When X

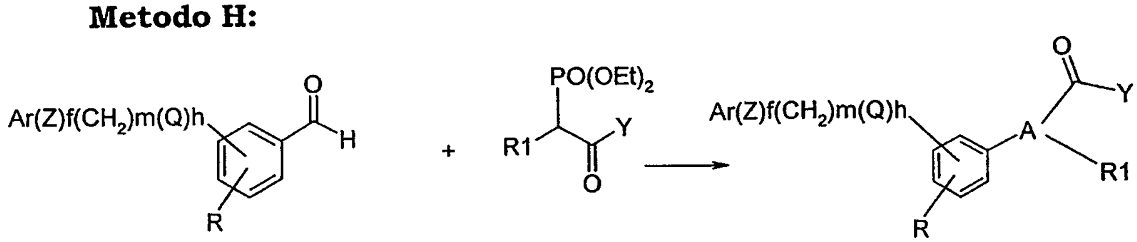
is an OH or SH group and Z_1 is an O group the reaction can be conducted as described in method C*. When X is an OC(O)Cl or SC(O)Cl group and Z_1 is an N group, the reaction is conducted in organic solvents such as $CHCl_3$, THF and the like, using a base such as triethylamine as the proton acceptor, at a temperature ranging from 0 to 60°C, preferably 25°C, for reaction times ranging from 2 to 24 hours, preferably 18 hours.

* In questi casi A, COY e R1 possono formare un ciclo =  

*In these cases, A, Coy and R1 may form a cycle =

In the case of formula (I) compounds in which $R_1 = OR_3$ and A = CH=C, method H described here below can be used.

Metodo H:



Iq Ir I

Unless otherwise specified, the meanings of the various groups are intended to coincide with those indicated in the general formula.

The general formula I compounds can be synthesised starting from compounds of general formula Iq and formula Ir (the latter obtained as described in *Tetrahedron*, ***1992**, 48 (19)*, 3991-4004), in aprotic solvents such as THF, in the presence of an inorganic base such as alcaline metal hydrides, preferably NaH, at a temperature ranging from 20 to 100°C, preferably ambient temperature, for reaction times ranging from 1 to 48 hours, preferably 20 hours.

In the case of formula (I) compounds in which A is alkanylilidene, these can be prepared from the corresponding formula (I) compounds where A is alkenylilidene.

Saturatedcompounds of general formula I can be obtained by reduction of the unsaturated compounds by catalytic hydrogenation in the presence of H_2, at a pressure ranging from atmospheric pressure to 60 psi, preferably 50 psi, and with catalysts such as metals supported on C, such as Pd/C, in percentages ranging from 1 to 20%, preferably 10%. The amount of catalyst used may fall within a range from 1 to 100% w/w, usually 10% w/w, in protic or aprotic solvents such as MeOH, dioxane and THF, preferably MeOH, for reaction times ranging from 18 hours to 3 days, preferably 24 hours. The reduction can also be conducted by means of hydrides such as $NaBH_4$ in organic solvents such as MeOH for reaction times ranging from 1 to 24 hours, preferably 2 hours, with a reaction temperature ranging from 0 to 80°C, preferably 25°C. An additional reduction method consists in the use of alkaline metals such as Mg in protic

solvents such as MeOH, EtOH and the like at a temperature ranging from 20 to 40°C, preferably 25°C, for reaction times ranging from 2 to 24 hours, preferably 6 hours.

Unless otherwise indicated, the starting compounds are commercially available or can be prepared according to conventional methods, following the guidelines provided in the examples. The following examples further illustrate the invention.

Example 1

<u>Preparation of diethyl 4-[2-(1-indolyl)ethoxy]benzylidene-malonate (ST1445)</u>

<u>Preparation of the intermediate product 1-(2-hydroxy-ethyl)indole</u>

The intermediate product, reported in *J. Med. Chem.*, **1998**, *41/10*, 1619-1639, was prepared according to the procedure described therein except for the duration of the reaction time (30 hours insetad of 30 minutes), starting from indole (5.00 g, 42.7 mmol), KOH (3.60 g, 64.1 mmol) and from 2-bromoethanol (6.40 g, 51.3 mmol) in 50 mL of anhydrous DMSO, at T = 25-30°C, to give 5.00 g of oily product (yield = 73%).

<u>Preparation of the intermediate product 1-(2-methane-sulphonyloxyethyl)indole</u>

To a solution of 1-(2-hydroxyethyl)indole (1.00 g, 6.20 mmol), in 25 mL of anhydrous dichloromethane were added anhydrous

pyridine (736 mg, 9.30 mmol) and, dropwise, methanesulphonyl chloride (1.06 g, 9.30 mmol). The reaction was left to stir at T = 50°C for 2 hours. After this time period the mixture was evaporated in vacuo and the residue dissolved in ethyl acetate (50 mL) and washed with H_2O (50 mL). The organic solution separated from the aqueous solution was washed with a solution of HCl 0.1N (2 x 50 mL) and with H_2O (2 x 50 mL). The organic solution was dried on anhydrous Na_2SO_4 and evaporated, and the residue was triturated with 100 mL of hexane to give 1.10 g of solid product after filtration (yield = 74%). Melting point (Mp) = decomposes at 75°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.61; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H), 7.38 (d, 1H), 7.22 (m, 2H), 7.18 (m, 2H), 6.57 (d, 1H), 4.50 (m, 4H), 2.60 (s, 3H); Elemental Analysis (E.A.) conforms for C_{11} H_{13} N O_3 S.

<u>Preparation of the intermediate product 4-[2-(1-indolyl)ethoxy]benzaldehyde</u>

The intermediate product, reported in *J. Med. Chem.* **1998**, *41(10)*, 1619-1639, was prepared with a different synthesis procedure, starting from the intermediate product 1-(2-methanesulphonyloxyethyl)indole (1.40 g, 5.85 mmol) and from 4-hydroxybenzaldehyde (880 mg 6.86 mmol) with NaH (190 mg, 7.87 mmol) in 30 mL of anhydrous DMF. The reaction mixture was left under continual stirring at a temperature of 80°C for 18 hours. At the end of this time period H_2O (150 mL) was added to the mixture

and the product was extracted with ethyl acetate (3 x 150 mL). The organic extracts collected were dried on anhydrous Na_2SO_4 and the solvent evaporated in vacuo to obtain 1.50 g of product (yield = 96%).

Preparation of diethyl 4-[2-(1-indolyl)ethoxy]benzylidene-malonate (ST1445)

Method A

To a solution of 4-[2-(1-indolyl)ethoxy]benzaldehyde (1.40 g, 5.28 mmol) and diethylmalonate (845 mg, 5.28 mmol) in 15 mL of anhydrous toluene were added AcOH (47.2 mg, 0.79 mmol) and piperidine (66.9 mg, 0.79 mmol). The reaction mixture was left to reflux with Dean-Stark for 7 hours. After this time period the mixture was dried and the crude reaction product was purified by silica gel chromatography using AcOEt:hexane 3:7 as the eluent to give 1.50 g of oily product (yield = 70%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.66; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (m, 2H), 7.40 (m, 3H), 7.22 (d, 1H), 7.20 (d, 1H), 7.15 (t, 1H), 6.80 (d, 2H), 6.45 (d, 1H), 4.45 (t, 2H), 4.25 (m, 6H), 1.25 (m, 6H); HPLC: column Inertisil ODS-3 (5 μm) (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (70:30 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 19.47 min; Elemental Analysis (E.A.) conforms for $C_{24}H_{25}NO_5$.

Example 2

Preparation of diethyl 4-[2-(1-indolyl)ethoxy]benzylmalonate (ST1446)

ST1445, obtained as described in example 1, (0.90 g, 2.20 mmol) was dissolved in 30 mL of dioxane and subjected to catalytic hydrogenation (60 psi) with 10% Pd/C (90 mg) for 48 hours at ambient temperature. After this time period the suspension was filtered on celite and the filtrate evaporated in vacuo. The crude product was purified by flash chromatography on silica gel, using AcOEt:hexane 2:8 as the eluent, to give 380 mg of oily product (yield = 42%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.60; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, 1H), 7.30 (d, 1H), 7.18 (m, 2H), 7.00 (m, 3H), 6.70 (d, 2H), 6.45 (d, 1H), 4.42 (t, 2H), 4.20 (t, 2H), 4.05 (m, 4H) 3.45 (t, 1H) 3.05 (d, 2H), 1.15 (t, 6H); HPLC: column: Inertisil ODS-3 (5 μm) (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (70:30 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 19.16 min; Elemental Analysis (E.A.) conforms for $C_{24}H_{27}NO_5$.

Example 3

Preparation of dimethyl 4-[2-(1-indolyl)ethoxy]benzylidene-malonate (ST1443)

Method B

To a suspension of NaH (360 mg, 15.0 mmol) in anhydrous DMF (70 mL) was added, under N_2 flow, a solution of dimethyl 4-hydroxybenzylidenemalonate (3.00 g, 12.5 mmol) in 15 mL of anhydrous DMF. After clarification of the reaction mixture (30 minutes) a solution of 1-(2-methanesulphonyloxyethyl)indole was added, prepared as described in example 1, (2.90 g, 12.5 mmol), in 15 mL of anhydrous DMF, and the reaction mixture was left to stir for 18 hours at 70°C under N_2 flow. After this time period H_2O (300 mL) was added to the reaction and the product was extracted with ethyl acetate (3 x 100 mL). The organic solution was washed with H_2O and with a saturated solution of NaCl, dried on anhydrous Na_2SO_4 and evaporated dry in vacuo. The crude reaction product was purified by flash chromatography on silica gel using AcOEt:hexane 2:8 as the eluent to give 3.10 g of solid product (yield = 65%). Melting point (Mp) = 68-70°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.61; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (s, 1H), 7.62 (d, 1H), 7.40 (m, 3H), 7.20 (m, 3H), 6.82 (d, 2H), 6.50 (d, 1H), 4.50 (t, 2H), 4.30 (t, 2H), 3.80 (d, 6H); HPLC: column: Symmetry C18 (5 μm) (150 x 3.9 mm), mobile phase $CH_3CN:KH_2PO_4$ 50 mM (60:40 v/v), pH = 3, T = 30°C, flow rate = 0.5

mL/min, 205 nm UV detector, retention time = 12.75 min; Elemental Analysis (E.A.) conforms for $C_{22}H_{21}NO_5$.

Example 4

Preparation of dimethyl 4-[2-(1-indolyl)ethoxy]benzylmalonate (ST1444)

ST1443, prepared as described in example 3, (1.50 g, 3.90 mmol), was dissolved in 45 mL of dioxane and subjected to catalytic hydrogenation (60 psi) with 10% Pd/C (750 mg) for 24 hours at ambient temperature. The suspension was filtered on celite and the filtrate was evaporated in vacuo to give an oily residue that was purified by silica gel chromatography using AcOEt:hexane 2:8 as the eluent to give 0.90 g of oily product (yield = 60%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.63; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H), 7.40 (d, 1H), 7.20 (m, 2H), 7.10 (2d, 3H), 6.80 (d, 2H), 6.50 (d, 1H), 4.50 (t, 2H), 4.25 (t, 2H), 3.70 (s, 6H), 3.60 (t, 1H), 3.15 (d, 2H); HPLC: column: Symmetry C18 (5 μm) (150 x 3.9 mm), mobile phase CH_3CN:KH_2PO_4 50 mM (60:40 v/v), pH = 3, T = 30°C, flow rate = 0.5 mL/min, 205 nm UV detector, retention time = 13.15 min; Elemental Analysis (E.A.) conforms for $C_{22}H_{23}NO_5$.

Example 5

Preparation of 4-[2-(1-indolyl)ethoxy]benzylmalonic acid (ST1467)

To a solution of ST1444, prepared as described in example 3, (0.95 g, 2.50 mmol), in methanol (10 mL) and THF (5 mL), was added NaOH 2N (3 mL) and the reaction was left to stir at ambient temperature for 24 hours. After this time period the reaction was evaporated in vacuo, water (10 mL) was added to the residue, and the solution was extracted with AcOEt (2 x 10 mL). The aqueous phase was acidified with HCl 1 N to pH = 4 and the product was extracted with AcOEt (2 x 10 mL). The organic extracts were dried on anhydrous Na_2SO_4 and evaporated in vacuo. The residue was re-dissolved in AcOEt and precipitated with hexane to give 250 mg of product (yield = 28%); Melting point (Mp) = 112-114°C TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.28; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, 1H), 7.50 (d, 1H), 7.30 (d, 1H), 7.20 (t, 1H), 7.10 (m, 3H), 6.80 (d, 2H), 6.45 (d, 1H), 4.50 (t, 2H), 4.30 (t, 2H), 3.60 (t, 1H), 3.05 (d, 2H); HPLC: column: Symmetry C18 (5 μm) (150 x 3.9 mm), mobile phase $CH_3CN:KH_2PO_4$ 50 mM (55:45 v/v), pH = 4, T = 30°C, flow rate = 0.5 mL/min, 205 nm UV detector, retention time = 4.40 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{19}NO_5$, KF = 0.8% H_2O.

Example 6

Preparation of methyl (2S)-amino-2-[4-[2-(1-indolyl)ethoxy]phenyl]acetate (ST1539)

Preparation of the intermediate product 4-hydroxy-(2S)-α-phenylglycine hydrochloride methyl ester

To a solution of 4-hydroxy-(2S)-α-phenylglycine (5.00 g, 29.0 mmol) in MeOH (50 mL) was added $SOCl_2$ (7.20 g, 59.0 mmol). The reaction was left to stir at ambient temperature for 24 hours. The solvent was evaporated in vacuo and the residue triturated with diethyl ether to give 6.50 g of product as a white solid (yield = 100%); TLC: silica gel, eluent AcOEt:hexane 5:5, Frontal ratio (Fr) = 0.21; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, 2H), 6.90 (d, 2H), 5.20 (s, 1H), 3.80 (s, 3H).

Preparation of methyl (2S)-amino-2-[4-[2-(1-indolyl)ethoxy]-phenyl]acetate (ST1539)

The product was prepared as described in example 3 (*method B*) starting from 4-hydroxy (2S)-α-phenylglycine hydrochloride methyl ester (1.10 g, 5.00 mmol) and from 1-(2-methane-sulphonyloxyethyl)indole, prepared as described in example1 (1.20 g, 5.00 mol) in anhydrous DMF (50 mL), except for the amount of NaH (280 mg, 12.0 mmol), the reaction time (6 hours instead of 18 hours) and the eluent used in the purification by chromatography (AcOEt instead of AcOEt:hexane 2:8), to give 500 mg of oily product (yield = 31%); $[\alpha]_D^{20}$ = -7° (c = 0.1 in MeOH); TLC: silica gel, eluent

AcOEt:MeOH 9:1, Frontal ratio (Fr) = 0.51; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H), 7.40 (d, 1H), 7.22 (m, 4H), 7.10 (t, 1H), 6.80 (d, 2H), 6.55 (d, 1H), 4.50 (s+t, 3H), 4.30 (t, 2H), 3.70 (s, 3H); HPLC: column: Symmetry C18 (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:KH_2PO_4 50 mM (60:40 v/v), pH = 4.2, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 6.52 min; Elemental Analysis (E.A,) conforms for $C_{19}H_{20}N_2O_3$.

Example 7

Preparation of methyl 4-[2-(1-indolyl)ethoxyi]benzoate (ST1671)

The product was prepared as described in example 3 (*method B*) from 1-(2-methanesulphonyloxyethyl)indole, prepared as described in example 1 (0.95 g, 3.90 mmol), methyl 4-hydroxybenzoate (600 mg, 3.90 mmol) and NaH (114 mg, 4.70 mmol), in anhydrous DMF (10 mL), except for the reaction time (24 hours instead of 18 hours) and the eluent used in the purification by chromatography (AcOEt:hexane 1:9 instead of 2:8). The still impure product obtained was purified by chromatography on Amberlyst A21 resin using AcOEt as the eluent to give 540 mg of product as a white solid (yield = 47%); Melting point (Mp) = 70-73°C, TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.48; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (d, 2H), 7.65 (d, 1H), 7.40 (d, 1H), 7.20 (m, 3H), 6.90 (d, 2H), 6.60 (d,1H), 4.60 (t, 2H), 4.40 (t, 2H), 3.90 (s, 3H); HPLC: column: Symmetry (5 μm)-(250 x 4.6 mm), mobile phase

$CH_3CN:KH_2PO_4$ 50 mM (60:40 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 24.66 min; Elemental Analysis (E.A.) conforms for $C_{18}H_{17}NO_3$.

Example 8

Preparation of methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-propanoate (ST1626)

The product was prepared as decsribed in example 3 (*method B*) from 1-(2-methanesulphonyloxyethyl)indole, prepared as described in example 1, (1.10 g, 4.50 mmol), methyl 4-hydroxyphenylpropanoate (820 mg, 4.55 mmol) and NaH (142 mg, 5.90 mmol), except for the solvent (anhydrous acetonitrile (1.5 mL) instead of anhydrous DMF) and the eluent used in the purification by chromatography (AcOEt:hexane 1:9 instead of 2:8). The residue obtained was triturated further with hexane to eliminate traces of solvent, to give 270 mg of product as a white solid (yield = 19%); Melting point (Mp) = 85°C, TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.49; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H), 7.40 (d, 1H), 7.20 (m, 3H), 7.10 (d, 2H), 6.80 (d, 2H), 6.50 (d,1H), 4.50 (t, 2H), 4.30 (t, 2H), 3.82 (s, 3H), 2.90 (t, 2H), 2.60 (t, 2H); HPLC: column: Symmetry (5 μm) - (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 22.33 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{21}NO_3$.

Example 9

Preparation of methyl 2-[4-[2-(1-indolyl)ethoxy]phenyl]acetate (ST1627)

The product was prepared as described in example 3 (*method B*) from 1-(2-methanesulphonyloxyethyl)indole, prepared as described in example 1 (860 mg, 3.60 mmol), methyl 4-hydroxyphenylacetate (600 mg, 3.60 mmol) and NaH (112 mg, 4.70 mmol), except for the solvent (anhydrous acetonitrile (1.5 mL) instead of anhydrous DMF) and the eluent used in the purification by chromatography (AcOEt:hexane 1:9 instead of 2:8) to give 243 mg of product as a white solid (yield = 22%); Melting point (Mp) = 50-52°C, TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.46; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H), 7.40 (d, 1H), 7.20 (m, 5H), 6.80 (d, 2H), 6.55 (d,1H), 4.58 (t, 2H), 4.30 (t, 2H), 3.70 (s, 3H), 3.60 (s, 2H); HPLC: column: Symmetry (5 μm) - (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 17.38 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{19}NO_3$.

Example 10

Preparation of methyl 2-sulpho-2-[4-[2-(1-indolyl)ethoxy]-phenyl]acetate sodium salt (ST1706)

Preparation of the intermediate product methyl 4-hydroxy-α-sulphophenylacetate sodium salt

The product was prepared from 4-hydroxy-α-sulphophenylacetic acid sodium salt monohydrate (2.00 g, 7.34 mmol) disolved in MeOH (44 mL) with the addition of $SOCl_2$ (1.75 g, 14.6 mmol). The reaction mixture was left at ambient temperature for 24 hours After evaporation of the solvent in vacuo the residue was treated with diethyl ether (3 x 50 mL). The still impure final residue was purified by flash chromatography on silica gel using $CHCl_3$:MeOH 8:2 as the eluent to give 1.25 g of oily product (yield = 63.5%); ^{1}H NMR (D_2O, 300 MHz) δ 7.30 (d, 2H), 6.80 (d, 2H), 4.95 (s, 1H), 3.65 (s, 3H); Elemental Analysis (E.A.) conforms for $C_9H_{10}SO_6Na$; KF = 2.2% H_2O.

Preparation of methyl 2-sulpho-2-[4-[2-(1-indolyl)ethoxy]-phenyl]acetate sodium salt (ST1706)

The product was prepared as described in example 3 (*method B*) starting from methyl 4-hydroxy-sulphophenylacetate sodium salt (1.10 g, 4.10 mmol), 1-(2-methanesulphonyloxyethyl)indole, prepared as described in example 1, (0.98 g, 4.10 mmol), and NaH (147.6 mg, 6.15 mmol) in 3.4 mL of anhydrous DMF, except for the reaction time and the temperature (3 hours instead of 18 hours, at 120°C rather than at 80°C). The dark semisolid was treated with diethyl ether (200 mL) and the crude solid obtained was purified by flash chromatography on silica gel using $CHCl_3$:MeOH 9:1 as the eluent to give 400 mg of solid product (yield = 21.4%); Melting point (Mp) = 253-258°C (decomposes); TLC: silica gel, eluent $CHCl_3$:MeOH

7:3, Frontal ratio (Fr) = 0.58; ^1H NMR (CD_3OD_{d4}, 300 MHz) δ 7.55 (m, 4H), 7.25 (d, 1H), 7.18 (t, 1H), 7.00 (t, 1H) 6.80 (d, 2H), 6.42 (d, 1H), 4.85 (s, 1H), 4.50 (t, 2H), 4.30 (t, 2H), 3.70 (s, 3H); HPLC: column: Symmetry C18 (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:KH_2PO_4 50 mM (50:50 v/v), pH =3, T = 30°C, flow rate = 1 mL/min, 205 nm UV detector, retention time = 6.07 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{18}NO_6NaS$.

Example 11

Preparation of methyl (S)-2-benzoylamino-2-[4-[2-(1-indolyl)-ethoxy]phenyl]acetate (ST1709)

Preparation of the intermediate product methyl (S)-2-benzoylamino-2-(4-hydroxyphenyl)acetate

The product was prepared from 4-hydroxy-(2S)-α-phenylgyicine methyl ester hydrochloride, prepared as described in example 6, (1.24 g, 5.70 mmol) dissolved in DMF (30 mL), adding TEA (1.15 g, 11.4 mmol) and benzoyl chloride (896 mg, 6.38 mmol) to the solution at 0°C. The reaction mixture was left at ambient temperature for 18 hours. After this time period H_2O (100 mL) was added to the reaction and the product was extracted with ethyl acetate (3 x 30 mL). The organic solution was washed with H_2O (2 x 40 mL), dried on anhydrous Na_2SO_4 and evaporated dry in vacuo, to give 1.29 g of solid product (yield = 79%); Melting point (Mp) =

152°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, 2H), 7.50 (m, 3H), 7.20 (d, 2H), 6.80 (d, 2H), 5.70 (d, 1H), 3.80 (s, 3H).

Preparation of methyl (2S)-benzoylamino-2-[4-[2-(1-indolyl)-ethoxy]phenyl]acetate (ST1709)

The product was prepared as described in example 3 (*method B*) starting from methyl (2S)-benzoylamino-2-(4-hydroxy-phenyl)acetate (0.70 g, 2.50 mmol), 1-(2-methanesulphonyloxy-ethyl)indole, prepared as described in example 1 (0.58 g, 2.50 mmol) and NaH (72 mg, 3.00 mmol) for 24 hours (instead of 18 hours). In the processing CH_2Cl_2 was used for extraction of the product with water instead of ethyl acetate The chromatographic purification of the product was done using AcOEt:hexane 7:3 (instead of 2:8) as the eluent to give 530 mg of oily product (yield = 50%); $[\alpha]_D^{20}$ = -2.6° (c = 1% in $CHCl_3$); TLC: silica gel, eluent AcOEt:hexane 5:5, Frontal ratio (Fr) = 0.65; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, 2H), 7.60 (d, 1H), 7.55-7.10 (m, 9H), 6.82 (d, 2H), 6.50 (d, 1H), 5.70 (d, 1H), 4.50 (t, 2H), 4.22 (t, 2H), 3.75 (s, 3H); HPLC: column: Inertisil ODS-3 (5 μm) (250 x 4.6 mm), mobile phase $CH_3CN:KH_2PO_4$ 50 mM (65:35 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 13.57 min; Elemental Analysis (E.A.) conforms for $C_{26}H_{24}N_2O_4$, KF = 1.5% H_2O.

Example 12

Preparation of methyl 2-hydroxy-3-[4-[2-(1-indolyl)ethoxy]-phenyl]propanoate (ST1733)

Preparation of the intermediate product methyl 2-hydroxy-3-(4-hydroxy)phenyl)propanoate

The product was prepared from D,L 3-(4-hydroxyphenyl)lactic acid hydrate (500 mg, 2.76 mmol) dissolved in MeOH (30 mL) with gaseous HCl to saturation. The reaction solution was left at ambient temperature for 4 hours. After evaporation of the solvent in vacuo the oily residue was re-dissolved with diethyl ether and the solvent evaporated in vacuo, repeating the operation 3 times (3 x 10 mL) to give 540 mg of oily product (yield = 100%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 2H), 6.90 (d, 2H), 5.00 (brs, 1H), 4.45 (t, 1H), 3.80 (s, 3H), 3.00 (dd, 2H).

Preparation of methyl 2-hydroxy-3-[4-[2-(1-indolyl)ethoxy]-phenyl]propanoate (ST1733)

The product was prepared as described in example 3 (*method B*) starting from methyl 2-hydroxy-3-(4-hydroxyphenyl)propanoate (800 mg, 4.10 mmol) and 1-(2-methanesulphonyloxyethyl)indole, prepared as described in example 1 (970 mg, 4.10 mmol) and NaH (108 mg, 4.50 mmol) in 50 mL of anhydrous DMF, at 40°C for 24 hours (instead of at 70°C for 18 hours). In the processing the product was extracted with CH_2Cl_2 instead of ethyl acetate and the final residue was purified by chromatography using AcOEt:hexane

3:7 (instead of 2:8) as the eluent to give 270 mg of solid product (yield = 18%); Melting point (Mp) = 70-72°C; TLC; silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.22; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, 1H), 7.40 (d, 1H), 7.12 (m, 3H), 7.10 (d, 2H), 6.80 (d, 2H), 6.55 (d, 1H), 4.50 (t, 2H), 4.40 (brt, 1H), 4.22 (t, 2H), 3.80 (s, 3H), 3.00 (dq, 2H); HPLC: column: Inertisil ODS-3 (5 μm) - (250 x 4.6 mm), mobile phase CH_3CN:KH_2PO_4 50 mM (65:35 v/v), pH = as is, T= 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 9.39 min; Elemental Analysis (E.A.). conforms for $C_{20}H_{21}NO_4$.

Example 13

Preparation of dimethyl 4-[2-[4-(dimethylamino)phenyl]-ethoxy]benzylmalonate (ST1705)

Preparation of the intermediate product 1-methane-sulphonyloxy-2-[4-(dimethylamino)phenyl]ethyl

To a solution of 4-(dimethylamino)phenylethanol (500 mg, 3.02 mmol), in anhydrous dichloromethane (10 mL), were added TEA (336 mg, 3.33 mmol) and, dropwise, methanesulphonyl chloride (381 mg, 3.33 mmol) at 0°C. The reaction was left at ambient temperature for 18 hours. After this time period the mixture was evaporated in vacuo, the residue was extracted with AcOEt (100 mL) and the solution filtered. The organic solution was evaporated in vacuo to give 720 mg of oily product (yield = 98%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 2H), 6.70 (d, 2H), 4.40 (t, 2H), 3.00 (m, 8H), 2.85 (s, 3H).

Preparation of the intermediate product dimethyl 4-hydroxybenzylmalonate

The product was prepared from dimethyl 4-hydroxybenzylidenemalonate (5.00 g, 21.0 mmol) by catalytic hydrogenation with 10% Pd/C (500 mg) in MeOH, as described in the method in patent WO 94/13650 *Heterocyclic derivatives and their use in pharmaceuticals*, except for the duration of the reaction time (24 hours instead of 5 hours) and the pressure (50 psi instead of ambient pressure) to give 5.00 g of oily product (yield = 99%); the analytical data resemble those reported in the literature described.

Preparation of dimethyl 4-[2-[4-(dimethylamino)phenyl]-ethoxy]benzylmalonate (ST1705)

The product was prepared as described in example 3 (*method B*) starting from dimethyl 4-hydroxybenzylmalonate (708 mg, 2.97 mmol), 1-methanesulphonyloxy-2-[4-(dimethylamino)phenyl]ethyl (724 mg, 2.97 mmol) and NaH (71 mg, 2.97 mmol). The crude reaction product was purified by flash chromatography on silica gel using AcOEt:hexane 15:85 (instead of 2:8) as the eluent to give the oily product that was further purified by treatment with hexane to give 270 mg of product (yield = 24%); TLC: silica gel, eluent AcOEt:hexane 4:6, Frontal ratio (Fr) = 0.55; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, 2H), 7.12 (d, 2H), 6.80 (d, 2H), 6.75 (m, 2H), 4.10 (t, 2H), 3.70 (s, 6H), 3.60 (t, 1H), 3.18 (d, 2H), 3.00 (t, 2H), 2.90 (s, 6H); HPLC: column: Symmetry C18 (5 μm) (250 x 4.6 mm), mobile phase

$CH_3CN:H_2O$ (65:35 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 19.13 min; Elemental Analysis (E.A.) conforms for $C_{22}H_{27}NO_5$.

Example 14

Preparation of methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyanopropenoate (ST1462)

Preparation of the intermediate product methyl α-cyano-4-hydroxycinnamate

To a solution of α-cyano-4-hydroxycinnamic acid (20.0 g, 106 mmol) in MeOH (200 mL) was added $SOCl_2$ (24.9 g, 210 mmol). The reaction was left to stir at T = 60°C for 24 hours. The solvent was evaporated in vacuo and the residue triturated with diethyl ether to give 18.0 g of product as a pale yellow solid (yield = 85%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.28; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (s, 1H), 8.10 (d, 2H), 7.10 (d, 2H), 3.90 (s, 3H).

Preparation of methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyanopropenoate (ST1462)

Method C

To a solution of 1-(2-hydroxyethyl)indole, prepared as described in example 1, (1.00 g, 6.20 mmol) and methyl α-cyano-4-hydroxycinnamate (1.10 g, 5.60 mmol) in anhydrous THF (20 mL) were added DEAD (1.30 g, 7.3 mmol) and PPh_3 (1.90 g, 7.30 mmol).

The solution was left to stir at ambient temperature for 5 days. The residue obtained after evaporation of the solvent in vacuo was purified by flash chromatography on SiO_2 gel using AcOEt:hexane 2:8 as the eluent to give 850 mg of solid product (yield = 44%); Melting point (Mp) = 142-144°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.38; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (s, 1H), 7.90 (d, 2H), 7.60 (d, 1H), 7.35 (d, 1H), 7.10 (m, 2H), 7.05 (t, 1H), 6.80 (d, 2H), 6.45 (d, 1H), 4.50 (t, 2H), 4.25 (t, 2H), 3.80 (s, 3H); HPLC: column: Symmetry C18 (5 μm) - (150 x 3.9 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH = as is, T = 30°C, flow rate = 0.5 mL/min, 205 nm UV detector, retention time = 13.86 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{18}N_2O_3$.

Example 15

Preparation of methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyanopropanoate (ST1499)

ST1462, re-prepared as described in example 14 (1.30 g, 3.70 mol), was dissolved in 60 mL of THF and subjected to catalytic hydrogenation (15 psi) with 10% Pd/C (130 mg) for 24 hours. The suspension was filtered on celite, the filtrate evaporated in vacuo and the residue purified by flash chromatography on SiO_2 gel, using AcOEt:hexane 3:7 as the eluent to give 620 mg of oily product (yield = 48%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.42; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H), 7.40 (d, 1H), 7.20 (m,

5H), 6.80(d, 2H), 6.55 (d, 1H), 4.50(t, 2H), 4.30(t, 2H), 3.80 (s, 3H), 3.65 (t, 1H), 3.15 (m, 2H); HPLC: column: Symmetry C18 (5 μm) - (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (70:30 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 14.47 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{20}N_2O_3$.

Example 16

Preparation of dimethyl 4-[2-(3-indolyl)ethoxy]benzylidene-malonate (ST1474)

The product was prepared as described in example 14 (*method C*) starting from 3-(2-hydroxyethyl)indole, (2.50 g, 15.5 mmol), dimethyl 4-hydroxybenzylidenemalonate (3.30 g, 14.1 mmol), DEAD (3.20 g, 18.3 mmol) and PPh_3 (4.80 g, 18.3 mmol), except for the reaction time (4 days instead of 5 days) and the eluent used in the purification by chromatography (AcOEt:hexane 3:7 and isopropyl ether:hexane 6:4 instead of AcOEt:hexane 2:8) to give a solid residue which was crystallised with AcOEt and hexane to give 480 mg of product (yield = 9.5%); Melting point (Mp) = 105.7°C; TLC: silica gel, eluent AcOEt:hexane 1:1, Frontal ratio (Fr) = 0.65; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00 (brs,1H), 7.65 (s, 1H), 7.61 (d, 1H), 7.40 (m, 3H), 7.20 (m, 3H), 6.85 (d, 2H), 4.25 (t, 2H), 3.82 (d, 6H), 3.22 (t, 2H); HPLC: column: Symmetry (5 μm) (150 x 3.9 mm), mobile phase $CH_3CN:KH_2PO_4$ 50 mM (50:50 v/v), pH = 3, T = 30°C, flow rate = 0.5

mL/min, 205 nm UV detector, retention time = 22.85 min; Elemental Analysis (E.A.) conforms for $C_{22}H_{21}O_5$.

Example 17

Preparation of dimethyl 4-[2-(1-naphthyl)ethoxy]benzyl-malonate (ST1475)

The product was prepared as described in example 14 (*method C*) starting from 1-(2-hydroxyethyl)naphthalene (1.50 g, 8.70 mmol), dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13, (1.90 g, 7.90 mmol), DEAD (1.90 g, 11.3 mmol) and PPh_3 (2.90 g, 11.3 mmol), except for the reaction time (1 day instead of 5 days) to give 1.90 g of oily product after purification (yield = 61%); TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.42; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, 1H), 7.90 (d, 1H), 7.70 (t, 1H), 7.47 (m, 2H), 7.42 (d, 2H), 7.10 (d, 2H) 6.80 (d, 2H), 4.25 (t, 2H), 3.62 (s, 6H), 3.60 (m, 3H), 3.20 (d, 2H); HPLC: column: Symmetry (5 μm) (150 x 3.9 mm), mobile phase $CH_3CN:KH_2PO_4$ 50 mM (55:45 v/v), pH = 3, T = 30°C, flow rate = 0.7 mL/min, 205 nm UV detector, retention time = 28.46 min; Elemental Analysis (E.A.) conforms for $C_{24}H_{24}O_5$.

Example 18

Preparation of dimethyl 4-[2-(2-pyridyl)ethoxy]benzylmalonate (ST1476)

The product was prepared as described in example 14 (*method C*) starting from 2-(2-hydroxyethyl)pyridine (800 mg, 6.40 mmol), dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13, (1.70 g, 6.90 mmol), DEAD (1.40 g, 8.00 mmol) and PPh_3 (2.10 g, 8.00 mmol), except for the reaction time (3 days instead of 5 days) and the eluent used in the purification by chromatography (AcOEt:hexane [3:7 instead of 2:8]) to give 850 mg of oily product (yield = 38%); TLC: silica gel, eluente AcOEt:hexane 1:1, Frontal ratio (Fr) = 0.36; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, 1H), 7.60 (td, 1H), 7.22 (d, 1H), 7.12 (m, 1H), 7.08 (d, 2H), 6.80 (d, 2H), 4.32 (t, 2H), 3.70 (s, 6H), 3.60 (t, 1H), 3.22 (t, 2H) 3.15 (d, 2H); HPLC: column: Symmetry (5 μm) (150 x 3.9 mm), mobile phase CH_3CN:KH_2PO_4 50 mM (25:75 v/v), pH = 3, T = 30°C, flow rate = 0.5 mL/min, 205 nm UV detector, retention time = 11.71 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{21}NO_5$, KF = 3.14% H_2O.

Example 19

Preparation of dimethyl 4-[2-(4-chlorophenyl)ethoxy]benzylmalonate (ST1493)

The product was prepared as described in example 14 (*method C*) starting from 2-(4-chlorophenyl)ethanol (700 mg, 4.60 mmol),

dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13, (1.20 g, 5.00 mmol), DEAD (1.10 g, 5.90 mmol) and PPh_3 (1.60 g, 5.90 mmol), except for the reaction time (3 days instead of 5 days) and the eluent used in the purification by chromatography (AcOEt:hexane [3:7 instead of 2:8]) to give 800 mg of oily product (yield = 47%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.47; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22 (q, 4H), 7.11 (d, 2H), 6.80 (d, 2H), 4.20 (t, 2H), 3.70 (s, 6H), 3.6 (t, 1H), 3.15 (d, 2H) 3.05 (t, 2H); HPLC: column: Symmetry (5 μm) (150 x 3.9 mm), mobile phase CH_3CN:KH_2PO_4 50 mM (55:45 v/v), pH = 5.5, T = 30°C, flow rate = 1.0 mL/min, 205 nm UV detector, retention = 23.42 min; Elemental Anaysis (E.A.) conforms for $C_{20}H_{21}ClO_5$.

Example 20

Preparation of 5-[4-[2-(4-chlorophenyl)ethoxy]phenyl-methylene]thiazolidine-2,4-dione (ST1862)

Preparation of the intermediate product 4-[2-(4-chloro-phenyl)ethoxy]benzaldehyde

The product was prepared as described in example 14 (*method C*) starting from 4-hydroxybenzaldehyde (2.00 g, 16.4 mmol), 2-(4-chlorophenyl)ethanol (2.80 g, 18.0 mmol), PPh_3 (5.57 g, 21.3 mmol) and DEAD (3.70 g, 21.3 mmol), except for the reaction time (one night instead of 5 days). 2.60 g of product were obtained after

purification (yield = 61%); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.90 (s, 1H), 7.80 (d, 2H), 7.30 (dd, 4H), 6.90 (d, 2H), 4.20 (t, 2H), 3.10 (t, 2H).

Preparation of 5-[4-[2-(4-chlorophenyl)ethoxy]phenyl-methylene]thiazolidine-2,4-dione (ST1862)

The product was prepared as described in example 1 (*method A*) from 4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (708 mg, 2.70 mmol) in 20 mL of anhydrous toluene, with thiazolidine-2,4-dione (320 mg, 2.70 mmol), acetic acid (21 mg, 0.35 mmol) and piperidine (29.8 mg, 0.35 mmol), except for the reaction time (5 hours instead of 7 hours). After cooling the mixture, yellow product crystals were separated which were left for 30 minutes at 0°C, then filtered, triturated first with cold toluene and then with water, and then dried. 786 mg of product were obtained (yield = 81%); Melting point (Mp) = 202-203°C; TLC: silica gel, eluent CH_2Cl_2:CH_3OH 9:1, Frontal ratio (Fr) = 0.6; ^1H NMR ($DMSO_{d6}$, 300 MHz) δ 7.70 (s, 1H), 7.50 (d, 2H), 7.30 (s, 4H), 7.10 (d, 2H), 4.25 (t, 2H), 3.05 (t, 2H); HPLC: column: LunaC_{18} (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase: $NH_4H_2PO_4$ 0.1M:CH_3CN (3:7 v/v), pH = as is, flow rate = 1 mL/min, 205 nm UV detector, retention time = 11.25 min; Elemental Analysis (E.A.) conforms for $C_{18}H_{14}NO_3SCl$

Example 21

Preparation of 5-[4-[2-(4-chlorophenyl)ethoxy]phenylmethyl]-thiazolidine-2,4-dione (ST1864)

To a suspension of ST1862, prepared as described in example 20, (600 mg, 1.67 mmol), in anhydrous MeOH (20 mL), was added piecemeal in small portions Mg in powder form (607 mg, 25.0 mmol). The reaction mixture was left for 5 hours at 25°C. After this time period the solvent was evaporated, water was added to the residue and acidified to pH 2 with a solution of HCl 1 N, and the aqueous phase was extracted with CH_2Cl_2. The pooled organic phases were washed with a saturated solution of NaCl, dried on anhydrous sodium sulphate and evaporated dry in vacuo. The residue thus obtained was purified by silica gel chromatography using $CHCl_3$:CH_3OH 99.5:0.5 as the eluent to give the still impure product which was recrystallised with methanol to give 180 mg of product (yield = 30%); Melting point (Mp) = 147-148°C; TLC: silica gel, eluent $CHCl_3$:CH_3OH 9.95:0.05, Frontal ratio (Fr) = 0.16; ^1H NMR ($DMSO_{d6}$, 300 MHz) δ 12.00 (brs, 1H), 7.40 (s, 4H), 7.20 (d, 2H), 6.90 (d, 2H), 4.90 (m, 1H), 4.20 (t, 2H), 3.30 (m, 2H), 3.00 (m, 2H); HPLC: column: LunaC$_{18}$ (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase: $NH_4H_2PO_4$ 0,05M:CH_3CN (4:6 v/v), pH = 4, flow rate 1 mL/min, 205 nm UV detector, retention time = 14.31 min; Elemental Analysis (E.A.) conforms for $C_{18}H_{16}NO_3SCl$.

Example 22

<u>Preparation of dimethyl 3-[2-(4-chlorophenyl)ethoxy]-benzylmalonate (ST1863)</u>

<u>Preparation of the intermediate product dimethyl 3-hydroxy-benzylidenemalonate</u>

The product was prepared as described in example 1 (*method A*) starting from 3-hydroxybenzaldehyde (3.02 g, 24.7 mmol), dimethylmalonate (2.83 mL, 24.7 mmol), piperidine (314 mg, 3.68 mmol) and glacial acetic acid (221 mg, 3.68 mmol), except for the reaction time (5 hours instead of 7). 3.91 g of product were obtained after purification (yield = 67%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (s, 1H), 7.30 (m, 1H), 6.90 (m, 3H), 3.90 (s, 6H).

<u>Preparation of the intermediate product dimethyl 3-hydroxy-benzylmalonate</u>

3-Hydroxybenzylidenemalonate (1.51 g, 6.40 mmol) was solubilised in 40 mL of methanol and added with 151 mg of 10% Pd/C. The mixture was then subjected to catalytic hydrogenation at 50 psi at ambient temperature for 18 hours. After this time period the mixture was filtered on celite and the organic phase evaporated in vacuo. The residue thus obtained was purified by silica gel chromatography using hexane:ethyl acetate 8:2 as the eluent. 1.31 g of product were obtained (yield = 86%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (t, 1H), 6.80 (m, 3H), 3.60 (s, 7H), 3.20 (d, 2H).

Preparation of dimethyl 3-[2-(4-chlorophenyl)ethoxy]benzyl-malonate (ST1863)

The product was prepared as described in example 14 (*method C*) starting from 3-hydroxybenzylmalonate (664 mg, 2.80 mmol), 2-(4-chlorophenyl)ethanol (435 mg, 2.80 mmol), triphenylphosphine (953 mg, 3.64 mmol), and DEAD (572 μL, 3.64 mmol) except for the reaction time (one night instead of 5 days). 700 mg of product were obtained after purification (yield = 66%); TLC: silica gel, eluent: hexane:ethyl acetate 8:2, Frontal ratio (Fr) = 0.35; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (m, 5H), 6.70 (m, 3H), 4.10 (t, 2H), 3.70 (s, 6H), 3.65 (t, 1H), 3.20 (d, 2H), 3.00 (t, 2H); HPLC: column: Luna C_{18} (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase: $NH_4H_2PO_4$ 0,05M:CH_3CN (4:6 v/v), pH = 4, flow rate 1 mL/min, 205 nm UV detector, retention time = 25.72 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{21}ClO_5$.

Example 23

Preparation of dimethyl 3-[2-(phenyl)ethoxy]benzylmalonate (ST1895)

ST1863, prepared as described in example 22 (470 mg, 1.20 mmol), was dissolved in 25 mL of methanol and subjected to catalytic hydrogenation at 60 psi with 10% Pd/C (50 mg) for 72 hours at ambient temperature. The suspension was filtered on celite, and the filtrate was evaporated in vacuo to give 95 mg of product

(yield = 22%); TLC: silica gel, eluent hexane:ethyl acetate 8:2, Frontal ratio (Fr) = 0.29; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 6H), 6.75 (m, 3H), 4.15 (t, 2H), 3.70 (s+t, 7H), 3.20 (d, 2H), 3.10 (t, 2H); HPLC: column: Inertisil ODS-3 (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase CH_3CN:H_2O (70:30 v/v), pH = 3.5, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 13.63 min; KF = 0.4% H_2O; Elemental Analysis (E.A.) conforms for $C_{20}H_{22}O_5$.

Example 24

Preparation of dimethyl 3-[N-(4-trifluoromethyl-benzyl)carbamoyl]-4-methoxybenzylmalonate (ST1933)

Preparation of the intermediate product methyl 5-formyl-2-methoxybenzoate acid

The product was prepared according to the procedure described in EP 0846693A1 starting from 5-formylsalicylic acid (2.00 g, 12.0 mmol) and iodomethane (10.2 g, 72.0 mmol) in DMF (45 mL) with K_2CO_3 (3.50 g, 25.2 mmol) to obtain 1.59 g of product (yield = 68%) with analytical data coinciding with those reported in the reference literature.

Preparation of the intermediate product 5-formyl-2-methoxybenzoic acid

The product was prepared according to the procedure described in EP 0846693A1 starting from methyl 5-formyl-2-methoxybenzoate (2.35 g, 12.1 mmol) in absolute AcOH (33 mL) with

concentrated HCl (33 mL) to obtain 1.59 g of product (yield = 73%) with analytical data coinciding with those reported in the reference literature.

Preparation of the intermediate product dimethyl-3-carboxy-4-methoxybenzylidenemalonate

The product was prepared according to the procedure described in example 1 (*method A)* starting from 5-formyl-2-methoxybenzoic acid (800 mg, 4.44 mmol) in 32 mL of anhydrous toluene, with dimethylmalonate (586 mg, 4.44 mmol), piperidine (57 mg, 0.67 mmol) and glacial acetic acid (40.2 mg, 0.67 mmol), except for the reaction time (5 hours instead of 7). At the end of this time period the mixture was cooled and, after 30 minutes at 4°C, crystals were separated which were filtered and triturated several times with toluene. 870 mg of product were obtained (yield = 67%); ^1H NMR ($DMSO_{d6}$, 300 MHz) δ 7.90 (s, 1H), 7.80 (s, 1H), 7.70 (d, 1H), 7.20 (d, 1H), 3.90 (s, 3H), 3.80 (d, 6H).

Preparation of the intermediate product dimethyl 3-[N-(4-trifluoromethylbenzyl)carbamoyl]4-methoxybenzylidenemalonate

Method E

To the solution of dimethyl-3-carboxy-4-methoxybenzylidene-malonate (620 mg, 2.10 mmol) in anhydrous DMF (6.2 mL) were added under N_2 flow 4-trifluoromethylbenzylamine (368 mg, 2.10 mmol), diethylphosphorocyanidate (377 mg, 2.10 mmol) and triethylamine (234 mg, 2.31 mmol). The reaction mixture was left at

ambient temperature under N_2 flow for 24 hours. After this time period the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was then washed with HCl 1N, NaOH 1N and water, dried on anhydrous sodium sulphate and evaporated in vacuo. The residue thus obtained was purified by silica gel chromatography using hexane:ethyl acetate 6:4 as the eluent. 249 mg of product were obtained (yield = 26%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 8.10 (brs, 1H), 7.70 (s, 1H), 7.50 (m, 5H), 6.90 (d, 1H), 4.70 (d, 2H), 3.90 (s, 3H), 3.80 (d, 6H).

<u>Preparation of dimethyl 3-[N-(4-trifluoromethylbenzyl)-carbamoyl]4-methoxybenzylmalonate (ST1933)</u>

Dimethyl 3-[N-(4-trifluoromethylbenzyl)carbamoyl] 4-methoxybenzylidenemalonate (148 mg, 0.33 mmol) was solubilised in methanol (18 mL) and added with 74 mg of 10% Pd/C. The mixture thus obtained was hydrogenated at 57 psi for 18 hours at ambient temperature. After this time period the suspension was filtered on celite and the filtrate dried by evaporating the solvent in vacuo to give 140 mg of product as a white solid (yield = 94%); Melting point (Mp) = 126-128°C; TLC: silica gel, eluent hexane:ethyl acetate 6:4, Frontal ratio (Fr) = 0.2; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (m, 1H), 8.10 (d, 1H), 7.60 (d, 2H), 7.50 (d, 2H), 7.30 (dd, 1H), 6.90 (d, 1H), 4.70 (d, 2H), 3.90 (s, 3H), 3.70 (s+t, 7H), 3.20 (d, 2H). HPLC: column: Inertisil - ODS 3 (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase CH_3CN:H_2O (70:30 v/v), flow rate = 0.75 mL/min, 205 nm

UV detector, retention time = 8.85 min; KF =1.55% H_2O; Elemental Analysis (E.A.) conforms for $C_{22}H_{22}F_3NO_6$.

Example 25

Preparation of dimethyl 4-methoxy-3-[2-(4-chlorophenyl)-ethoxy]benzylmalonate (ST1861)

Preparation of the intermediate product dimethyl 3-hydroxy-4-methoxybenzylidenemalonate

The product was prepared according to the procedure described in example 1 (*method A)* starting from 3-hydroxy-4-methoxybenzaldehyde (3.00 g, 19.7 mmol), dimethylmalonate (2.60 g, 19.7 mmol), piperidine (251 mg, 2.95 mmol) and glacial acetic acid (177 mg, 2.95 mmol) in 120 mL of anhydrous toluene, except for the eluent used in the purification by chromatography (hexane:ethyl acetate 8:2 instead of 7:3). 5.20 g of product were obtained (yield = 98%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (s, 1H), 7.00 (m, 2H), 6.90 (d, 1H), 5.60 (brs, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H).

Preparation of the intermediate product dimethyl 3-hydroxy-4-methoxybenzylmalonate

Dimethyl 3-hydroxy-4-methoxybenzylidenemalonate (5.20 g, 19.5 mmol) in 180 mL of methanol was hydrogenated at 60 psi with 10% Pd/C (520 mg) for 18 hours at ambient temperature. After this time period the reaction mixture was filtered on celite and the

solvent was evaporated in vacuo. 4.90 g of product were obtained (yield = 93.5%); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.70 (m, 3H), 3.90 (s, 3H), 3.70 (s, 6H), 3.60 (t, 1H), 3.20 (d, 2H).

Preparation of dimethyl 4-methoxy-3-[2-(4-chlorophenyl)-ethoxy]benzylmalonate (ST1861)

The product was prepared according to the procedure described in example 14 (*method C)* starting from dimethyl 3-hydroxy-4-methoxybenzylmalonate (900 mg, 3.38 mmol) with 2-(4-chlorophenyl)ethanol (582 mg, 3.79 mmol), triphenylphosphine (1.15 g, 4.39 mmol) and DEAD (765 mg, 4.39 mmol) in 9 mL of anhydrous THF, except for the reaction time (one night instead of 5 days) and the eluent used in the purification by chromatography (hexane:ethyl acetate 7:3 instead of 8:2). 550 mg of product were obtained (yield = 40%); Melting point (Mp) = 55-56°C; TLC: silica gel, eluent hexane:ethyl acetate 7:3, Frontal ratio (Fr) = 0.8; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 4H), 6.75 (m, 3H), 4.20 (t, 2H), 3.80 (s, 3H), 3.70 (s, 6H), 3.60 (t, 1H), 3.10 (m, 4H); HPLC: column: Symmetry C_{18} (5 μm) (3.9 x 150 mm), T = 30°C, mobile phase $CH_3CN:NH_4H_2PO_4$ (50:50 v/v), flow rate 0.75 mL/min, pH = 3.2, 205 nm UV detector, retention time = 23.23 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{23}ClO_6$.

Example 26

Preparation of dimethyl 3-(2-phenylethoxy)-4-methoxy benzylmalonate (ST1892)

To a solution of ST1861 (475 mg, 1.16 mmol), prepared as described in example 25, in 25 mL of methanol, was added 10% Pd/C (48 mg) and the resulting suspension was left under H_2 at 50 psi for 2 days at ambient temperature. After this time period the suspension was filtered on celite and the solvent evaporated in vacuo. The resiude obtained was purified by silica gel chromatography using hexane:ethyl acetato 8:2 as the eluent to give 130 mg of product (yield = 30%); TLC: silica gel, eluent hexane:ethyl acetate 6:4, Frontal ratio (Fr) = 0.55; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 6.75 (m, 3H), 4.20 (t, 2H), 3.80 (s, 3H), 3.70 (s, 6H), 3.60 (t, 1H), 3.10 (m, 4H); HPLC: column: Inertisil ODS – 3 (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase CH_3CN:$NH_4H_2PO_4$ 50 mM (50:50 v/v), flow rate = 0.75 mL/min, pH = 3.2, 205 nm UV detector, retention time = 8.92 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{24}O_6$.

Example 27

Preparation of dimethyl 4-[2-(4-methoxyphenyl)ethoxy]benzylmalonate (ST1893)

The product was prepared as described in example 14 (*method C)* starting from dimethyl 4-hydroxybenzylmalonate, prepared as

described in example 13 (600 mg, 2.52 mmol), 2-(4-methoxyphenyl)-ethanol (383 mg, 2.52 mmol), DEAD (568 mg, 3.27 mmol) and triphenylphosphine (856 mg, 3.27 mmol) in 15 mL of THF, except for the reaction time (one night instead of 5 days). 277 mg of product were obtained (yield = 29.5%); TLC: silica gel, eluent hexane:ethyl acetate 8:2; Frontal ratio (Fr) = 0.2; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 2H), 7.10 (d, 2H), 6.80 (m, 4H), 4.10 (t, 2H), 3.80 (s, 3H), 3.70 (s, 6H), 3.60 (t, 1H), 3.15 (d, 2H), 3.00 (t, 2H); HPLC: Column: Inertisil ODS - 3 (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase $CH_3CN:H_2O$ (60:40 v/v), flow rate 0.75 mL/min, pH = as is, 205 nm UV detector, retention time = 23.93 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{24}O_6$.

Example 28

Preparation of dimethyl 4-[3-(4-methoxyphenyl)propyloxy]-benzylmalonate (ST1894)

The product was prepared as described in example 14 (*method C)* starting from dimethyl 4-hydroxybenzylmalonate (600 mg, 2.52 mmol), prepared as described in example 13, with 3-(4-methoxyphenyl)-1-propanol (419 mg, 2.52 mmol), DEAD (568 mg, 3.27 mmol) and triphenylphosphine (857 mg, 3.27 mmol), in 15 mL of anhydrous THF, except for the reaction time which was one night instead of 5 days. 400 mg of product were obtained (yield = 41.1%); TLC: silica gel, eluent hexane:ethyl acetate 8:2; Frontal ratio (Fr) =

0.22; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (dd, 4H), 6.80 (dd, 4H), 3.90 (t, 2H), 3.80 (s,3H), 3.70 (s, 6H), 3.60 (t, 1H), 3.20 (d, 2H), 2.70 (t, 2H), 2.00 (m, 2H); HPLC: column: Inertisil ODS - 3 (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase CH_3CN:H_2O (60:40 v/v), flow rate 0.75 mL/min, pH = as is, 205 nm UV detector, retention time = 32.46 min; KF = 0.15% H_2O; Elemental Anlaysis (E.A.) conforms for $C_{22}H_{26}O_6$.

Example 29

Preparation of dimethyl 4-[2-(2-naphthyl)ethoxy]benzyl-malonate (ST1985)

The product was prepared according to the procedure described in example 14 (*method C)* starting from dimethyl 4-hydroxybenzylmalonato (476 mg, 2 mmol), prepared as described in example 13, 2-naphthalene-ethanol (344 mg, 2 mmol), DEAD (451 mg, 2,6 mmol) and triphenylphosphine (681 mg, 2,6 mmol), in 15 mL of anhydrous THF, except for the reaction time which was 2 days instead of 5 days and the eluent used in the purification by chromatography (hexane:ethyl acetate 9:1 instead of 8:2). The product thus obtained was further purified by crystalisation with isopropanol. 167 mg of product were obtained (yield = 21.3%); Melting point (Mp) = 68.5°C; TLC: silica gel, eluent hexane:ethyl acetate 8:2; Frontal ratio (Fr) = 0.7; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 7.40 (m, 3H), 7.10 (d, 2H), 6.90 (d, 2H), 4.20 (t, 2H), 3.70 (s,

6H), 3.60 (t, 1H), 3.20 (t, 2H), 3.10 (d, 2H); HPLC: Column: Symmetry-C_{18} (3.5 μm) (4.6 x 75 mm), T = ambient, mobile phase $CH_3CN:H_2O$ (60:40 v/v), flow rate 0.9 mL/min, pH = as is, 205 nm UV detector, retention time = 10.80 min; KF = 0.3% H_2O; Elemental Analysis (A.E.) conforms for $C_{24}H_{24}O_5$.

Example 30

Preparation of ethyl (2S)-2-benzoylamino-3-[4-[(4-methoxy-benzyl)carbamoyl]oxyphenyl]propanoate (ST1500)

Method D

The product was prepared from 4-methoxy benzylisocyanate (400 mg, 2.24 mmol) and N-benzoyl-L-tyrosine ethyl ester (700 mg, 2.24 mmol) dissolved in anhydrous THF (5 mL). NEt_3 (20 μL) was added to the solution and the reaction was left to stir for 18 hours at ambient temperature. The solution was evaporated to give 980 mg of product as a white solid (yield = 92%); Melting point (Mp) = 149-151°C; $[a]_D^{20}$ = +69.3 (c = 0.5% in $CHCl_3$); TLC: silica gel, eluent AcOEt:CH_2Cl_2 2:8, Frontal ratio (Fr) = 0.61; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, 2H), 7.50 (m, 3H), 7.30 (d, 2H), 7.10 (dd, 4H), 6.90 (d, 2H), 6.60 (d, 1H), 5.30 (m, 1H), 5.05 (q, 1H), 4.40 (d, 2H), 4.20 (q, 2H), 3.80 (s, 3H) 3.25 (m, 2H), 1.30 (t, 3H); HPLC: column: Symmetry (5 μm) (250 x 4.6 mm), mobile phase $CH_3CN:KH_2PO_4$ 50 mM (50:50 v/v), pH = as is, T= 30°C, flow rate = 0.75 mL/min, 205

nm UV detector, retention time = 19.16 min; KF = 0.8% H_2O; Elemental Analysis (E.A.) conforms for $C_{27}H_{28}N_2O_6$.

Example 31

<u>Preparation of dimethyl 4-[[(4-methoxybenzyl)carbamoyl]oxy]-benzylmalonate (ST1538)</u>

The product was prepared as described in example 30 (*method D)* starting from 4-methoxy benzylisocyanate (400 mg, 2.58 mmol) and dimethyl 4-hydroxybenzylmalonate, preparede as described in example 13 (700 mg, 3.02 mmol) in anhydrous THF (10 mL) and NEt_3 (20 μL), except for the fact that the residue obtained after evaporation of the reaction solvent was purified by flash chromatography on silica gel, using AcOEt:hexane 3:7 as the eluent, to give 740 mg of white solid (yield = 72%); Melting point (Mp) = 78.6°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.22; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 6.90 (d, 2H), 5.20 (m, 1H), 4.40 (d, 2H), 3.80 (s, 3H) 3.70 (s, 6H), 3.60 (t, 1H), 3.20 (d, 2H); HPLC: column: Symmetry (5 μm) - (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (50:50 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 16.12 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{23}NO_7$.

Example 32

Preparation of dimethyl 4-[[(4-trifluorotolyl)carbamoyl]oxy]-benzylmalonate (ST1620)

The product was prepared as described in example 30 (*method D)* starting from 4-trifluorotolyl isocyanate (410 mg, 2.19 mmol) and dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13 (600 mg, 2.52 mmol) in anhydrous THF (10 mL) and NEt_3 (20 µL), except for the fact that the residue obtained after evaporation of the reaction solvent was purified by flash chromatography on silica gel, using AcOEt:hexane 3:7 as the eluent, to give 350 mg of product as a white solid (yield = 37.1%); Melting point (Mp) = 109.1°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.44; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (q, 4H), 7.20 (d, 2H), 7.10 (d, 3H), 3.70 (s, 6H), 3.60 (t, 1H), 3.20 (d, 2H); HPLC: column: Symmetry (5 µm) (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 16.44 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{18}F_3NO_6$.

Example 33

Preparation of dimethyl 4-[[(2,4-dichlorophenyl)carbamoyl]oxy]-benzylmalonate (ST1818)

The product was prepared as described in example 30 (*method D)* starting from 2,4-dichlorophenylisocyanate (73 mg, 0.38 mmol)

and dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13 (100 mg, 0.42 mmol) in anhydrous THF (3 mL), with NEt_3 (10 μL), except for the fact that the residue obtained after evaporation of the reaction solvent was purified by flash chromatography on silica gel, using AcOEt:hexane 2:8 as the eluent, to give 120 g of product as a white solid (yield = 74%); Melting point (Mp) = 84°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.39; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (brd, 1H), 7.40 (m, 2H), 7.22 (m, 3H), 7.15 (d, 2H), 3.70 (s+t, 7H), 3.20 (d, 2H); HPLC: column: Inertisil ODS-3 (5 μm) - (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 28.13 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{17}Cl_2NO_6$.

Example 34

Preparation of dimethyl 4-[[(4-chlorophenyl)carbamoyl]oxy]-benzylmalonate (ST1696)

The product was prepared as described in example 30 (*method D)* starting from 4-chlorophenylisocyanate (560 mg, 3.65 mmol) and dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13, (1.00 g, 4.20 mmol) in anhydrous THF (16.6 mL), with NEt_3 (20 μL), except for the fact that after evaporation of the solvent the reaction residue was dissolved in AcOEt (130 mL) and extracted with a solution of NaOH 0.1 N (3 x 50 mL). The residue obtained

after evaporation of the solvent was purified by flash chormatography on silica gel, using AcOEt:hexane 2:8 as the eluent to give 550 mg of product as a white solid (yield = 38%); Melting point (Mp) = 125-127°C; TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.37; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d + s, 2H), 7.30-7.20 (m, 4H), 7.10 (d, 2H), 6.90 (brs, 1H), 3.70 (s, 6H), 3.65 (t, 1H), 3.20 (d, 2H); HPLC: column: Symmetry C_{18} (5 μm) - (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (65:35 v/v), pH = as is, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 14.78 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{18}ClNO_6$.

Example 35

<u>Preparation of dimethyl 4-[2-(pyridinio)ethoxy]benzyl-malonate methanesulphonate (ST1799)</u>

<u>Preparation of the intermediate product dimethyl 4-[2-(hydroxy)ethoxy]benzylidenemalonate</u>

To dimethyl 4-hydroxybenzylidenemalonate (2.00 g, 8.47 mmol) in anhydrous DMF (40 mL) was added NaH (244 mg, 10.2 mmol) and after approximately 30 minutes 2-bromoethanol (1.37 g, 11.0 mmol). The reaction mixture was left at a temperature of 70°C for 24 hours. After this time period H_2O (200 mL) was added to the mixture and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The organic phase washed with H_2O (2 x 50 mL) was dried on anhydrous Na_2SO_4 and then evaporated to give 2.00 g of oily

product (yield = 84%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (s, 1H), 7.40 (d, 2H), 6.90 (d, 2H), 4.10 (t, 2H), 4.00 (t, 2H), 3.85 (d, 6H).

Preparation of the intermediate product dimethyl 4-[2-(hydroxy)ethoxy]benzylmalonate

The product was prepared from dimethyl 4-[2-(hydroxy)ethoxy]benzylidenemalonate (4.50 g, 16.0 mmol) by catalytic hydrogenation with 10% Pd/C (500 mg) in MeOH (120 mL) in an H_2 atmosphere (50 psi) for 24 hours. After this time period, the solution was filtered on celite and the solvent evaporated to give 4.20 g of oily product (yield = 93%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 2H), 6.85 (d, 2H), 4.10 (t, 2H), 3.95 (t, 2H), 3.70 (s, 3H), 3.65 (t, 1H), 3.20 (d, 2H).

Preparation of the intermediate product dimethyl 4-[2-(methanesulphonyl)ethoxy]benzylmalonate

To dimethyl 4-[2-(hydroxy)ethoxy]benzylmalonate (2.00 g, 7.00 mmol) in CH_2Cl_2 (50 mL) were added anhydrous pyridine (1.66 g, 21.0 mmol) and mesyl chloride (2.43 g, 21.0 mmol), dropwise at 0°C. At the end of the additions the mixture was left at 50°C for 6 hours. After evaporation of the solvent the residue was re-dissolved in AcOEt (100 mL) and the organic phase was washed with H_2O (2 x 50 mL), then with HCl 1N (2 x 50 mL) and again with H_2O to neutral pH. The organic phase dried on anhydrous Na_2SO_4 was evaporated to give 2.02 g of oily product (yield = 80%); ^1H NMR ($CDCl_3$, 300

MHz) δ 7.10 (d, 2H), 6.85 (d, 2H), 4.60 (t, 2H), 4.22 (d, 2H), 3.70 (s, 3H), 3.65 (t, 1H), 3.20 (d, 2H), 3.10 (s, 3H).

Preparation of dimethyl 4-[2-(pyridinio)ethoxy]benzylmalonate methanesulphonate (ST1799)

Method F

The product was prepared from dimethyl 4-[2-(methanesulphonyl)ethoxy]benzylmalonate (960 mg, 2.60 mmol) dissolved in pyridine (15 mL). The reaction mixture was left for 18 hours at 75°C. After evaporation of the solvent the oily residue was washed with diethyl ether. The still impure final residue was purified by flash chromatography on silica gel using $CHCl_3$:MeOH 5:5 as the eluent to give 940 mg of oily product (yield = 82.3%); TLC: silica gel, eluent CHCl 4.2 : CH_3OH 2.8 : isopropanol 0.7 : CH_3COOH 1.05 : H_2O 1.05, Frontal ratio (Fr) = 0.48; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.40 (brd, 2H), 8,42 (brt, 1H), 8.00 (brd, 2H), 7.05 (d, 2H), 6.75 (d, 2H), 5.35 (m, 2H), 4.5 (m, 2H), 3.70 (s, 6H), 3.60 (t, 1H), 3.10 (d, 2H), 2.80 (s, 3H); HPLC: column: Spherisorb - SCX (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:$NH_4H_2PO_4$ 50 mM (40:60 v/v), pH = 3.5, T = 30°C, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 18.65 min; KF = 4.5% H_2O; Elemental Analysis (E.A.) conforms for $C_{19}H_{22}NO_5 \cdot CH_3O_3S$.

Example 36

Preparation of dimethyl 4-[[(4-nitrophenyl)carbamoyl]oxy]-benzylmalonate (ST1865)

The product was prepared as described in example 30 (*method D*) starting from dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13 (180 mg, 0.75 mmol), 4-nitrophenylisocyanate (124 mg, 0.75 mmol) in anhydrous THF (4 mL) and NEt_3 (20 μL), except for the fact that the residue obtained after evaporation of the reaction solvent was purified by flash chromatography on silica gel using hexane:AcOEt 1:1 as the eluent. 221 mg of product were obtained (yield = 73%); Melting point (Mp) = 128-130°C; TLC: silica gel, eluent hexane:AcOEt 1:1, Frontal ratio (Fr) = 0.55; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 2H), 7.60 (d, 2H), 7.30 (d, 2H), 7.10 (d, 2H), 3.70 (s+t, 7H), 3.25 (d, 2H); HPLC: column: luna C_{18}, (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase $NH_4H_2PO_4$ 0,05M:CH_3CN 4:6 (v/v), pH = 4, flow rate = 1 mL/min, 205 nm UV detector, retention time = 8.56 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{18}N_2O_8$.

Example 37

Preparation of dimethyl 3-[[(4-methoxybenzyl)carbamoyl]oxy]-benzylmalonate (ST1907)

The product was prepared as described in example 30 (*method D*) starting from dimethyl 3-hydroxybenzylmalonate, prepared as

described in example 22 (200 mg, 0.84 mmol), p-methoxybenzylisocyanate (188 mg, 1.16 mmol) and NEt_3 (20 μL) in anhydrous THF (5 mL), except for the reaction time which was 72 hours instead of 18 hours and for the fact that after evaporation of the solvent in vacuo the residue was purified by silica gel chromatography using hexane:AcOEt 7:3 as the eluent. 181 mg of product were obtained (yield = 54%); Melting point (Mp) = 62-64°C; TLC: silica gel, eluent hexane:AcOEt 6:4, Frontal ratio (Fr) = 0.36; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 4H), 7.00 (m, 2H), 6.90 (d, 2H), 5.20 (brm, 1H), 4.40 (m, 2H), 3.80 (s, 3H), 3.70 (s+t, 7H), 3.20 (d, 2H); HPLC: column: Symmetry - C_{18}, (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase $CH_3CN:H_2O$ 1:1 (v/v), pH = as is, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 17.58 min; KF = 0.18% H_2O; Elemental Analysis (E.A.) conforms for $C_{21}H_{23}NO_7$.

Example 38

Preparation of dimethyl 3-[[(4-butylphenyl)carbamoyl]oxy]-benzylmalonate (ST1908)

The product was prepared as described in example 30 *(method D)* starting from dimethyl 3-hydroxybenzylmalonate, prepared as described in example 22 (200 mg, 0.84 mmol), p-butylphenylisocyanate (174 mg, 1.0 mmol) and 20 μL of NEt_3 in 5 mL of anhydrous THF, except for the fact that after 36 hours a further 52.5 mg (0.30 mmol) of p-butylphenylisocyanate were added

and the reaction was left at ambient temperature for another 4 days. The solvent was evaporated in vacuo and the residue purified by silica gel chromatography using hexane:AcOEt 8:2 as the eluent. 130 mg of product were obtained (yield = 37.5%); Melting point (Mp) = 53-54°C; TLC: silica gel, eluent hexane:AcOEt 8:2, Frontal ratio = 0.26; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, 1H), 7.20 (m, 2H), 7.10 (m, 5H), 6.80 (brs, 1H), 3.70 (s, 6H) 3.65 (t, 1H), 3.20 (d, 2H) 2.60 (t, 2H), 1.60 (m, 2H), 1.30 (m, 2H), 0.90 (t, 3H); HPLC: column: Symmetry - C_{18}, (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase CH_3CN:H_2O 7:3 (v/v), pH = as is, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 16.17 min; Elemental Analysis (E.A.) conforms for $C_{23}H_{27}NO_6$.

Example 39

Preparation of dimethyl 4-[[(4-butylphenyl)carbamoyl]oxy]-benzylmalonate (ST1909)

The product was prepared as described in example 30 *(method D)* starting from dimethyl 4-hydroxybenzylmalonate, prepared as described in example 13 (200 mg, 0.84 mmol), p-butylphenylisocyanate (220 mg, 1.26 mmol) and NEt_3 (20 μL) in 5 mL of anhydrous THF, except for the reaction time which was 24 hours instead of 18 hours and the fact that after evaporation of the solvent in vacuo the product was purified by silica gel chromatography using hexane:AcOEt 8:2 as the eluent to give 129

mg of product (yield = 37%); Melting point (Mp) = 90-92°C; TLC: silica gel, eluent hexane:AcOEt 8:2, Frontal ratio (Fr) = 0.23; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 3H), 7.10 (d, 2H), 7.00 (m, 3H), 6.80 (brs, 1H), 3.70 (s, 6H) 3.65 (t, 1H), 3.25 (d, 2H), 2.60 (t, 2H), 1.60 (m, 2H), 1.35 (m, 2H), 0.90 (t, 3H); HPLC: column: Symmetry - C_{18}, (5 μm) (4.6 x 250 mm), T = 30°C, mobile phase $CH_3CN:H_2O$ 7:3 (v/v), pH = as is, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 15.96 min; KF = 0.52% H_2O; Elemental Analysis (E.A.) conforms for $C_{23}H_{27}NO_6$.

Example 40

Preparation of dimethyl 3-[[(4-chlorophenyl)carbamoyl]oxy]-benzylmalonate (ST1856)

The product was prepared as described in example 30 (*method D)* starting from dimethyl 3-hydroxybenzylmalonate (800 mg, 3.36 mmol) prepared as described in example 22, 4-chlorophenyl-isocyanate (774 mg, 5.04 mmol) and NEt_3 (20 μL) in 30 mL of anhydrous THF, except for the fact that after evaporating the solvent in vacuo, the residue was treated with ethyl acetate, filtered and the filtrate evaporated in vacuo. The residue obtained was purified by two silica gel chromatographies, the first using $CHCl_3$:hexane 8:2 and the second hexane:ethyl acetate 7:3 as the eluent to give 520 mg of product (yield = 39.6%); Melting point (Mp) = 79-80°C; TLC: silica gel, eluent hexane:ethyl acetate 6:4, Frontal ratio (Fr) = 0.6; ^1H

NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, 1H), 7.30 (m, 3H), 7.10 (m, 2H), 6.90 (brs, 1H), 3.70 (s+t, 7H), 3.25 (d, 2H); HPLC: column: Luna C_{18} (5 μm) (4.6 x 75 mm), T = 50°C, mobile phase NaH_2PO_4 0,05M:CH_3CN (50:50 v/v), flow rate = 1 mL/min, pH = as is, 205 nm UV detector, retention time = 24.34 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{18}ClNO_6$.

Example 41

Preparation of (Z)-2-ethoxy-3-[4-[2-(4-chlorophenyl)ethoxy]-phenyl]ethyl propenoate (ST2135) and of (E)-2-ethoxy-3-[4-[2-(4-chlorophenyl)ethoxy]phenyl]ethyl propenoate (ST2136)

Preparation of triethyl phosphonodiazoacetate

The product was prepared as described in *Tetrahedron*, **1992**, *48 (19)*, 3991-4004 starting from triethyl phosphonoacetate (8.60 g, 38.1 mmol), 80% NaH (1.04 g, 41.86 mmol) and tosylazide (7.50 g, 38.1 mmol) to give 6.60 g of product (yield = 69%). The analytical data were as reported in the literature.

Preparation of triethyl 2-ethoxyphosphonoacetate

The product was prepared according to the procedure described in *Tetrahedron*, **1992**, *48 (19)*, 3991-4004 starting from triethyl phosphonodiazoacetate (5.00 g, 19.9 mmol), absolute ethanol (36 mL), and bivalent rhodium acetate dimer (88.3 mg, 0.199 mmol) to obtain 3.20 g of product (yield = 60%); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.30-4.20 (m, 7H), 3.70 (dq, 2H), 1.40 (m, 12H).

<u>Preparation of (Z)-2-ethoxy-3-[4-[2-(4-chlorophenyl)-ethoxy]-phenyl]ethyl propenoate (ST2135) and of (E)-2-ethoxy-3-[4-[2-(4-chlorophenyl)ethoxy]phenyl]ethyl propenoate (ST2136)</u>

Method H

Triethyl 2-ethoxyphosphonoacetate (3.1 g, 11.5 mmol) was added at 0°C to a suspension of 80% NaH (384 mg, 12.78 mmol) in anhydrous THF (20 mL) and after approximately 30 minutes at ambient temperature 4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (2.4 g, 9.2 mmol) was added, prepared as described in example 20, dissolved in anhydrous THF (20 mL). At the end of the addition the reaction mixture was left to stir at ambient temperature for 20 hours. After evaporation of the solvent in vacuo the residue was purified by two SiO_2 gel chromatographies, the first using AcOEt:hexane 2:8, and the second AcOEt:hexane 5:95 as the eluent. 2.70 g of a mixture of the two isomers were obtained (yield = 63%), which in subsequent preparations was used as is in the synthesis of ST2211 (example 43) and ST2130 (example 42). To isolate the Z and E isomers, the mixture was further purified by two SiO_2 gel, chromatographies, the first using AcOEt:hexane 5:95 and the second CH_2Cl_2 as the eluent to give 330 mg of ST 2135 (Z isomer) as a semisolid (yield = 9.6%) and 380 mg of ST 2136 (E isomer) as an oily product (yield = 11%).

Analytical data for ST2135 (Z isomer)

TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.32; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, 2H), 7.22 (dd, 4H), 6.95 (s, 1H), 6.85 (d, 2H), 4.30 (q, 2H), 4.20 (t, 2H), 4.00 (q, 2H), 3.10 (t, 2H), 1.40 (t, 6H); HPLC: column: Inertisil ODS-3 C18 (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:H_2O (85:15 v/v), pH = as is, T = ambient, flow rate = 0.9 mL/min, 205 nm UV detector, retention time = 16.67 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{23}ClO_4$.

Analytical data for ST2136 (E isomer)

TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.36; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (dd, 4H), 7.10 (d, 2H), 6.80 (d, 2H), 6.10 (s, 1H), 4.20 (q + t, 4H), 3.90 (q, 2H), 3.05 (t, 2H), 1.40 (t, 3H), 1.18 (t, 3H); HPLC: column: Inertisil ODS-3 C18 (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:H_2O (85:15 v/v), pH = as is, T = ambient, flow rate = 0.9 ml/min, 205 nm UV detector, retention time = 10.79 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{23}ClO_4$.

Example 42

Preparation of (R,S)-2-ethoxy-3-[4-[2-(phenyl)ethoxy]phenyl]-ethyl propanoate (ST 2130)

To a solution of a mixture of ST 2135 and ST 2136 (600 mg, 1.6 mmol), obtained as described in example 41, in absolute ethanol (20 mL) was added 10% Pd/C (60 mg) and the mixture was left in an

H_2 atmosphere at 40 psi, at ambient temperature for 6 hours. After filtration on celite the solvent was evaporated in vacuo and the residue purified by chromatography on SiO_2 gel using hexane:AcOEt 95:5 as the eluent to give 470 mg of product (yield = 86%); TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.46; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (dd, 4H), 7.18 (d, 2H), 6.80 (d, 2H), 4.20 (t, 4H), 3.95 (t, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 3.10 (t, 2H), 2.90 (d, 2H), 1.22 (t, 3H), 1.18 (t, 3H); HPLC: column: Inertisil ODS-3 C18 (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:H_2O (85:15 v/v), pH = as is, T = ambient, flow rate = 0.9 mL/min, 205 nm UV detector, retention time = 8.98 min; Elemental Analysis (E.A.) conforms for $C_{21}H_{26}O_4$.

Example 43

Preparation of (R,S)-2-ethoxy-3-[4-[2-(4-chlorophenyl)ethoxy]-phenyl]methyl propanoate (ST 2211)

To a solution of a mixture of ST 2135 and ST 2136 (1.15 g, 3.06 mmol), obtained as described in example 41, in anhydrous methanol (73 mL) were added Mg in powder form (1.17 g) and a few crystals of I_2, and the mixture was left at ambient temperature for 6 hours. After this time period the solvent was evaporated, water was added to the residue and acidified to pH 2 with a solution of HCl 1 N, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried on anhydrous sodium sulphate and the solvent was

evaporated in vacuo. The residue was purified by silica gel chromatography using AcOEt:hexane 5:95 as the eluent to give 790 mg of oily product (yield = 71%); TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.42; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 4H), 7.20 (d, 2H), 6.80 (d, 2H), 4.20 (t, 2H), 3.95 (t, 1H), 3.70 (s, 3H), 3.60 (m, 1H), 3.40 (m, 1H), 3.10 (t, 2H), 3.00 (d, 2H), 1.20 (t, 3H); HPLC: column: Inertisil ODS-3 C18 (5 μm) (250 x 4.6 mm), mobile phase CH_3CN:H_2O (85:15 v/v), pH = as is, T = ambient, flow rate = 1 mL/min, 205 nm UV detector, retention time = 6.56 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{23}ClO_4$.

Example 44

Preparation of dimethyl 4-[2-(2,3-dimethyl-1-indolyl)ethoxy]-benzylmalonate (ST2206)

Preparation of the intermediate product 2,3-dimethyl-1(2-benzyloxyethyl)indole

To 2,3 dimethyl-1-indole (2.00 g, 13.8 mmol) in anhydrous DMSO (80 mL) were added triturated KOH (1.55 g, 27.6 mmol) and benzyl 2-bromoethylether (5.80 g, 27.6 mmol). The reaction mixture was left at ambient temperature for 20 hours. At the end of this time period H_2O (200 mL) was added to the mixture and the product was extracted with ethyl acetate (3 x 100 mL). The organic extracts were dried on anhydrous Na_2SO_4 and the solvent was evaporated in vacuo to give 3.20 g of oily product (yield = 83%); ^1H NMR ($CDCl_3$, 300

MHz) δ 7.55 (d, 1H), 7.30-7.10 (m, 8H), 4.42 (s, 2H), 4.30 (t, 2H), 3.80 (t, 2H), 2.40 (s, 3H), 2.30 (s, 3H).

Preparation of the intermediate product 2,3-dimethyl-1-(2-hydroxyethyl)indole

The product was prepared from 2,3-dimethyl-1-(2-benzyloxyethyl)indole (3.20 g, 11.5 mmol) dissolved in absolute ethanol (100 mL), with 10% Pd/C (800 mg), under H_2 at 50 Psi, at ambient temperature for 4 days. After filtration of the reaction mixture on celite the organic solvent was evaporated in vacuo and the residue purified by silica gel chromatography using hexane:AcOEt 6:4 as the eluent to give 900 mg of product (yield = 44%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (brd, 1H), 7.30 (d, 1H), 7.15 (m, 2H), 4.30 (t, 2H), 3.95 (t, 2H), 2.40 (s, 3H), 2.30 (s, 3H).

Preparation of dimethyl 4-[2-(2,3-dimethyl-1-indolyl)ethoxy]-benzylmalonate (ST2206)

The product was prepared according to the procedure described in example 14 (*method C*) starting from dimethyl 4-hydroxybenzylmalonate (1.13 g, 4.76 mmol), prepared as described in example 13, 2,3-dimethyl-1-(2-hydroxyethyl)indole (900 mg, 4.76 mmol), DIAD (1.25 g, 6.2 mmol) and triphenylphosphine (1.62 g, 6.2 mmol), in 90 mL of anhydrous THF, except for the reaction time which was 1 day instead of 5 days and the eluent used in the purification, i.e. hexane:ethyl acetate 7:3 instead of 8:2. The product was further purified by means of two silica gel chomatographies, the

first using hexane:ethyl acetate 9:1 and the second CH_2Cl_2 as the eluent to give 506 mg of product (yield = 26%); TLC: silica gel, eluent AcOEt:hexane 3:7, Frontal ratio (Fr) = 0.50; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (d, 1H), 7.30 (d, 1H), 7.10 (m, 2H), 7.05 (d, 2H), 6.70 (d, 2H), 4.50 (t, 2H), 4.20 (t, 2H), 3.70 (s, 3H), 3.60 (t, 1H), 3.10 (d, 2H), 2.40 (s, 3H), 2.20 (s, 3H); HPLC: column: Inertisil-ODS-3 (5 μm) (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (80:20 v/v), pH = as is, T = ambient, flow rate = 0.9 mL/min, 205 nm UV detector, retention time = 9.96 min; Elemental Analysis (E.A.) conforms for $C_{24}H_{27}NO_5$.

Example 45

Preparation of (R,S)-2-ethoxy-3-[3-[2-(4-chlorophenyl) ethoxy]phenyl]methyl propanoate (ST 2324)

Preparation of the intermediate product (Z,E)-2-ethoxy-3-[3-[2-(4-chlorophenyl)ethoxy]phenyl]ethyl propenoate

The product was prepared as described in example 41 (*method H*) starting from triethyl 2-ethoxyphosphonoacetate (3.6 g, 13.42 mmol), prepared as described in example 41, which was added at 0°C to a suspension of NaH 80% (480 mg, 15.96 mmol) in anhydrous THF (28 mL), and after approximately 30 minutes at ambient temperature 3-[2-(4-chlorophenyl)ethoxy]benzaldehyde (3.0 g, 11.50 mmol) was added, dissolved in anhydrous THF (20 mL). After evaporation of the solvent in vacuo the residue was purified to

give 1.29 g of a mixture of the two isomers (yield = 30%); TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.32; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, 2H), 7.22 (dd, 4H), 6.95 (s, 1H), 6.85 (d, 2H), 4.30 (q, 2H), 4.20 (t, 2H), 4.00 (q, 2H), 3.10 (t, 2H), 1.40 (t, 6H).

Preparation of (R,S)-2-ethoxy-3-[3-[2-(4-chlorophenyl)ethoxy]phenyl]-methyl propanoate (ST 2324)

To a solution of a mixture of (Z,E)-2-ethoxy-3-[3-[2-(4-chlorophenyl)ethoxy]phenyl]ethyl propenoate (1.29 g, 3.44 mmol) in anhydrous methanol (73 mL) were added Mg in powder form (1.65 g) and a few crystals of I_2, and the mixture was left at ambient temperature for 24 hours. After this time period the solvent was evaporated, water was added to the residue and acidified to pH 2 with a solution of HCl 1 N, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried on anhydrous sodium sulphate and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using AcOEt:hexane 5:95 as the eluent to give 916 mg of oily product (yield = 80%); TLC; silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.45; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 - 7.20 (m, 5H), 6.80 (m, 3H), 4.15 (t, 2H), 4.00 (t, 1H), 3.70 (s, 3H), 3.60 (m, 1H), 3.35 (m, 1H), 3.05 (t, 2H), 2.95 (d, 2H), 1.15 (t, 3H); HPLC: column: Inertisil ODS-3 C18 (5 μm) (250 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (85:15 v/v), pH = as is, T

= 30°C, flow rate = 1 mL/min, 205 nm UV detector, retention time = 6.42 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{23}ClO_4$.

Example 46

Preparation of 5-[3-[2-(4-chlorophenyl)ethoxy]phenylmethylene] thiazolidine-2,4-dione (ST2431)

The product was prepared as described in example 1 (*method A*) from 3-[2-(4-chlorophenyl)ethoxy]benzaldehyde (1.22 g, 4.70 mmol) in 33 mL of anhydrous toluene, with thiazolidine-2,4-dione (550 mg, 4.70 mmol), acetic acid (37 mg, 0.62 mmol) and piperidine (53 mg, 0.62 mmol) except for the reaction time (5 hours instead of 7 hours). After cooling the mixture, yellow product crystals were separated which were left for 30 minutes at 0°C, then filtered and triturated first with cold toluene and then with water, and then dried. 1.28 g of product were obtained (yield = 76%); Melting point (Mp) = 186-187°C; TLC: silica gel, eluent CH_3Cl:CH_3OH 9.8:0.2; Frontal ratio (Fr) = 0.45; ^1H NMR ($DMSO_{d6}$, 300 MHz) δ 12.60 (brs, 1H), 7.70 (s, 1H), 7.40-7.30 (m, 6H), 7.10 (m, 2H), 4.25 (t, 2H), 3.05 (t, 2H); HPLC: column: Symmetry C_{18} (5 μm) (4.6 x 150 mm), T = ambient, mobile phase: $NH_4H_2PO_4$ 0,05 M:CH_3CN (4:6 v/v), pH = as is, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 11.25 min; Elemental Analysis (E.A.) conforms for $C_{18}H_{14}NO_3SCl$

Example 47

Preparation of 5-[3-[2-(4-chlorophenyl)ethoxy]phenylmethyl]-thiazolidine-2,4-dione (ST2390)

To a suspension of ST2431, prepared as described in example 46 (900 mg, 2.50 mmol), in anhydrous MeOH (52 mL), was added piecemeal in small portions Mg in powder form (972 mg, 40.0 mmol). The reaction mixture was left for 5 hours at 25°C. After this time period the solvent was evaporated, water was added to the residue and acidified to pH 2 with a solution of HCl 1 N, and the aqueous phase was extracted with CH_2Cl_2. The pooled organic phases were washed with a saturated solution of NaCl, dried on anhydrous sodium sulphate and evaporated dry in vacuo. The residue thus obtained was purified by silica gel chromatography using $CHCl_3$ as the eluent to give a product which was still impure that was recrystallised with methanol and then purified again by silica gel chromatography using $CHCl_3$ as the eluent to give 255 mg of product (yield = 28%); Melting point (Mp) = 90-91°C; TLC: silica gel, eluent $CHCl_3$:CH_3OH 9.8:0.2, Frontal ratio (Fr) = 0.45; ^1H NMR ($DMSO_{d6}$, 300 MHz) δ 12.00 (brs, 1H), 7.40 (m, 5H), 7.20 (t, 1H), 6.80 (m, 3H), 4.90 (dd, 1H), 4.15 (t, 2H), 3.35 (m, 1H), 3.00 (m, 3H); HPLC: column: Symmetry C_{18} (5 μm) (4.6 x 250 mm), T = ambient, mobile phase: $NH_4H_2PO_4$ 0.05M:CH_3CN (4:6 v/v), pH = as is, flow rate 0.7 mL/min, 205 nm UV detector, retention time = 12.22 min; Elemental Analysis (E.A.) conforms for $C_{18}H_{16}NO_3SCl$.

Example 48

Preparation of dimethyl 3-[[(4-trifluorotolyl)carbamoyl]oxy] benzylmalonate (ST2413)

The product was prepared as described in example 30 (*method D)* starting from 4-trifluorotolyl isocyanate (1.29 g, 6.93 mmol) and dimethyl 3-hydroxybenzylmalonate, prepared as described in example 22, (1.10 g, 4.62 mmol) in anhydrous THF (30 mL) and NEt_3 (20 μL), except for the fact that the residue obtained after evaporation of the reaction solvent was purified by flash chromatography on silica gel, using AcOEt:hexane 8:2 as the eluent, to give 650 mg of product as a white solid (yield = 33%); Melting point (Mp) = 93-94°C; TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.13; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (m, 4H), 7.30 (m, 2H), 7.05 (m, 2H), 3.70 (s+t, 7H), 3.20 (d, 2H); HPLC: column: Symmetry C18 (5 μm) (150 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH = as is, T = ambient, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 8.77 min; Elemental Analysis (E.A.) conforms for $C_{20}H_{18}F_3NO_6$.

Example 49

Preparation of dimethyl 3-[[(2,4-dichlorophenyl)carbamoyl]-oxy]benzylmalonate (ST2424)

The product was prepared as described in example 30 (*method D)* starting from 2,4-dichlorophenylisocyanate (707 mg, 3.78 mmol)

and dimethyl 3-hydroxybenzylmalonate, prepared as described in example 22 (600 mg, 2.52 mmol) in anhydrous THF (7 mL), with NEt_3 (10 μL) except for the fact that the residue obtained after evaporation of the reaction solvent was purified by flash chromatography on silica gel, using AcOEt:hexane 2:8 as the eluent, to give 610 mg of product (yield = 56.9%); TLC: silica gel, eluent AcOEt:hexane 2:8, Frontal ratio (Fr) = 0.40; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 7.40 (m, 4H), 7.10 (m, 2H), 3.70 (s+t, 7H), 3.25 (d, 2H); HPLC: column: Symmetry C18 (5 μm) - (150 x 4.6 mm), mobile phase $CH_3CN:H_2O$ (60:40 v/v), pH= as is, T = ambient, flow rate = 0.75 mL/min, 205 nm UV detector, retention time = 9.51 min; Elemental Analysis (E.A.) conforms for $C_{19}H_{17}Cl_2NO_6$.

The compounds according to the invention described herein are useful as medicines, particularly for the preparation of medicines with serum glucose and serum lipid lowering activity. The preferred applications are the prophylaxis and treatment of diabetes, particularly type 2, and its complications, Syndrome X, the various forms of insulin resistance and hyperlipdaemias.

In a thoroughly advantageous manner, the compounds according to the invention described herein are endowed with good pharmacological activity, but present reduced liver toxicity.

Experiments have been conducted *in vivo* in diabetic mouse models and *in vitro* in adipocyte 3T3-L1 cell lines (reported in the literature in predictive assays for potential antidiabetic activity – see,

for example, Sarges et al., J Med Chem 39: 4783 - 4803, 1996, Luo et al., Diabetic Med 15: 367 - 374, 1998 and Bierer et al., J Med Chem 41: 894 - 901, 1998).

Pharmacological activity

Determination of glucose consumption in 3T3 - L1 cells

Glucose consumption was assessed in differentiated 3T3 - L1 cells.

Mouse fibroblasts (3T3 - L1) were seeded at a density of 5 x $10^3/cm^2$ and cultured on 12-well plates in 1 ml of DMEM containing glucose 25 mM and added with 10% CS, glutamine 4 mM, pyruvate 1 mM, penicillin 50 U/ml, and streptomycin 50 μg/ml, in an atmosphere humidified with 5% CO_2 at 37°C.

Two to three days after confluence, differentiation was induced with the addition of 1.5 ml of DMEM containing 3-isobutyl-1-methylxanthine (IBMX) 0.5 mM, dexamethazone 1 μM and porcine insulin 10 μg/ml in glucose 25 mM and 10% FBS.

After 2 days, the cells were exposed to the same medium without IBMX and dexamethazone for another 2 days.

The cells were then maintained in DMEM containing glucose 25 mM and 10% FBS over the next few days, with changes of culture medium at intervals of 2-3 days (*Clancy BM and Czech MP, J. Biol. Chem., 265: 12434 - 12443, 1990; Frost SC and Lane M.D, J. Biol. Chem. 260: 2645 - 2652, 1985*).

The cells were used 10-12 days after induction of differentiation, as monitored by evaluating triglyceride accumulation.

For the assessment of glucose consumption, the cells were incubated for 22 hours in DMEM containing glucose 25 mM, insulin 0.25 nM (submaximal concentration) and the compounds (1, 5, 10, 25 μM) dissolved in DMSO (final concentration 0.1%).

Rosiglitazone was used as a positive control.

The analysis of the glucose in the medium was done with the aid of a Cobas Mira S autoanalyzer (Roche), using the HK 125 Glucose Kit (ABX Diagnostics).The glucose concumprion stimulated by the products was evaluated as % increase compared to the control compound.

Taking compound 22 as an example, Table 1 gives the lowest concentration of those assayed to induce a 40% increase in glucose consumption compared to the control compound (rosiglitazone).

From the results obtained it can be deduced that the compounds investigated were capable of increasing glucose consumption in 3T3 - L1 cells to a similar extent to that achieved by the reference compound (rosiglitazone).

Table 1

Compound	μM*
Rosiglitazone	5
Example 22	1

Antidiabetic and serum lipid lowering activity in db/db mice

Mutations in laboratory animals have made it possibile to develop models that present non-insulin-dependent diabetes associated with obesity, hyperlipidaemia and insulin-resistance and that enable us to test the efficacy of new antidiabetes compounds *(Reed and Scribner, Diabetes, obesity and metabolism 1: 75 - 86, 1999).*

A genetically diabetic mouse model much used by the pharmaceutical companies is the C57BL/KsJ db/db mouse.

The genetic basis of this model is a defect in the leptin receptor gene, which causes leptin resistance and leads to hyperphagia, obesity, hyperinsulinaemia and insulin resistance, with subsequent symptoms of insufficient insular secretion and hyperglycaemia *(Kodama et al., Diabetologia 37: 739 - 744, 1994; Chen et al., Cell 84: 491 - 495, 1996).*

Since hyperglycaemia is accompanied by obesity and insulin resistance, the db/db mouse has characteristics that resemble those of type 2 diabetes in man and is useful for assaying insulin-sensitising compounds.

The thiazolidinediones constitute one class of such compounds *(Day, Diabet. Med. 16: 179-192, 1999; Mudaliar and Herry, Annu. Rev. Mred. 52: 239 - 257, 2001, Drexler et al., Geriatrix 56: 20 - 33, 2001).*

Of the three thiazolidinediones launched on the market, troglitazone was withdrawn owing to its severe liver toxicity, while the other two compounds, rosiglitazone and pioglitazone, which are effective in reducing diabetic hyperglycaemia, are known to present weight gain, oedema, liver toxicity, increased LDL-cholesterol, and anaemia as side effects *(Schoonjans and Auwerx, The Lancet 355: 1008 - 1010, 2000; Peters, Am. J. Manag. Care 7: 587-595, 2001; Gale, The Lancet 357: 1870 - 1875, 2001).*

The C57BL/KsJ db/db mice in the experiments were supplied by Jackson Lab (via Ch. River). After 10 days of acclimatisation in standard conditions (22 ± 2°C; 55 ± 15% humidity; 15–20 air changes/hour; 12 hour light-dark cycle, with light from 7.00 a.m to 7.00 p.m), and on a standard 4 RF21 diet (Mucedola), blood samples were taken in postabsorption conditions (fasting from 8.30 a.m to 4.30 p.m.) from the caudal vein with the aid of a Jelco 22G catheter (Johnson and Johnson). Plasma levels of glucose, insulin, triglycerides, cholesterol, free fatty acids and urea were monitored to ensure a well-matched distribution of the mice in the treatment groups.

At the start of treatment, the animals' body weights were checked and arrangements were made for monitoring water and feed consumption.

The mice were treated orally twice daily (8.30 a.m. and 6.30 p.m.) for a fortnight.

The compounds were administered at a dose equivalent to 25 mg/kg of the compound in example 22 in 10 ml/kg of vehicle (CMC 1% containing Tween 80 0.5% in deionised H_2O). Rosiglitazone was administered at the dose of 5 mg/kg *(Lohray et al. J. Med Chem 41, 1619 - 1630, 1998).*

The animals were sacrificed (by decapitation) in postabsorption conditions (fasting from 9.30 a.m. to 4.30 p.m.) 7 hours after the last treatment. Serum levels of a number of important lipid and carbohydrate metabolism variables were measured.

The compounds according to the invention described herein show a good ability to reduce serum triglyceride levels in a manner similar to the reference compound rosiglitazone. Table 2, by way of an example, shows the serum lipid lowering activity of the compound in example 22 and of rosiglitazone.

The compounds, moreover, are, like rosiglitazone, also capable of lowering serum glucose levels (Table 3) and this is achieved with lesser changes in weight and transaminase (GPT) values, which is indicative of less liver damage (Table 4). By way of an example, Table 3 gives the serum glucose lowering activity of the example 22 compound and Table 4 the changes in weight and transaminase values in the same compound, again as compared to rosiglitazone. Furthermore, unlike rosiglitazone, the compounds according to the invention increase HDL-cholesterol levels. By way of an example, Table 4 gives the changes in HDL-cholesterol levels for the

compound in example 22 and for the reference compound rosiglitazone. An increase in HDL-cholesterol constitutes an indicator of PPARα agonism and of a reduced risk of atherosclerosis. PPARα agonism, in fact, increases fatty acid oxidation in the tissues, reducing the accumulation of intracellular triglycerides, which favour insulin resistance *(Virkamäki et al., Diabetes 50, 2337 - 2343, 2001; Mensink et al., Diabetes 50, 2545 - 2554, 2001; Kelley and Goodpaster, Diabetes Care 24, 933 - 941, 2001)*. It is known, for example, that the fibrates, which are PPARα agonists, not only lower hyperlipidaemia, but are also capable of improving insulin sensitivity *(Matsui et al., Diabetes 46, 348 - 353, 1997)*, atherosclerosis and cardiovascular damage *(Fruchart et al., Current Atherosclerosis Reports 3, 83 - 92, 2001)*, which is a serious complication and cause of death in the course of diabetic disease.

The usefulness of these compounds for correcting hyperlipidaemia, diabetes and the cardiovascular complications accompanying these disease conditions is evident.

Table 2

Serum lipid lowering activity in db/db mice

Compound	Dose (mg/kg)	Reduction of triglyceride levels %
Rosiglitazone	5	- 41 ▲
Example 22	25	- 47 ▲

Student's 't'-test: ▲ indicates $P < 0.001$ vs control.

Table 3

Serum glucose lowering activity in db/db mice

Compound	Dose (mg/kg)	Reduction of glucose levels %
Rosiglitazone	5	- 36 Δ
Example 22	25	- 32 Δ

Student's 't'-test: Δ indicates $P < 0.01$ vs control

Table 4

Weight gain and changes in GPT and HDL-cholesterol serum levels in db/db mice

Compound	Dose (mg/kg)	Weight gain %	Change in GPT levels %	Change in HDL-cholesterol levels %
Rosiglitazone	5	+ 22 ▲	+ 117 ▲	- 7
Example 22	25	+ 16 ▲	+ 38 ▲	+ 37 ▲

Student's 't'-test: ▲ indicates $P < 0.001$ vs control.

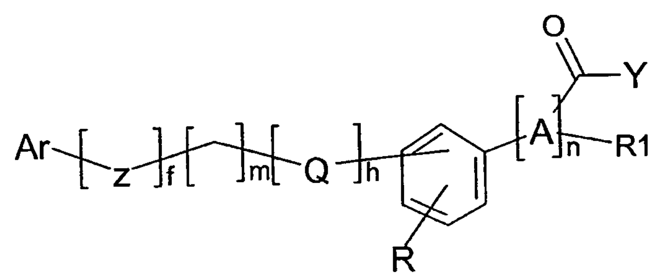
The subject of the invention described herein are pharmaceutical compositions containing as their active ingredient at least one formula (I) compound, or, said formula (I) compound or compounds in combination with other active ingredients useful in the treatment of the diseases indicated in the invention described herein, e.g. other products endowed with serum glucose and serum lipid lowering activity, also in separate dosage form or in forms suitable for combined therapies. The active principle according to the invention described herein will be in a mixture with suitable

vehicles and/or excipients commonly used in pharmacy, such as, for instance, those described in "Remington's Pharmaceutical Sciences Handbook", latest edition. The compositions according to the invention described herein will contain a therapeutically effective amount of the active ingredient. The dosages will be determined by the expert in the sector, e.g. the clinican or primary care physician, according to the type of disease to be treated and the patient's condition, or concomitantly with the administration of other active ingredients. By way of an example we may indicate dosages ranging from 0.1 to 200 mg/day.

Examples of pharmaceutical compositions are those that permit oral or parenteral, intravenous, intramuscular, subcutaneous and transdermal administration. Suitable pharmaceutical compositions for this purpose are tablets, rigid or soft capsules, powders, solutions, suspensions, syrups, and solid forms for extempore liquid preparations. Compositions for parenteral administration are, for example, all the intramuscular, intravenous and subcutaneous injectable forms, in the form of solutions, suspensions and emuslions. Liposomal formulations should also be mentioned. Also included are the forms characterised by controlled release of the active ingredient, whether as oral administration forms, tablets coated with suitable layers, microencapsulated powders, complexes with cyclodextrin, or depot forms, e.g. of the subcutaneous type, such as depot injections or implants.

CLAIMS

1. Formula (I) compounds:



I

where:

A is CH; alkanylilidene with 2 to 4 carbon atoms, particularly CH_2-CH; alkenylilidene with 2 to 4 carbon atoms, particularly CH=C;

Ar is monocyclic or bicyclic C_6-C_{10} aryl or heteroaryl, containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, possibly substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen; monocyclic, bicyclic or tricyclic arylalkyl or heteroarylalkyl containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, where the alkyl residue contains from 1 to 3 carbon atoms, said arylalkyl or heteroarylalkyl possibly substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy,

said alkyl and alkoxy possibly substituted by at least one halogen;

f is the number 0 or 1;

h is the number 0 or 1;

m is a whole number from 0 to 3;

n is the number 0 or 1 and if n is 0, R_1 is absent, and COY is directly bound to benzene);

Q and Z, which may be the same or different, are selected from the group consisting of NH, O, S, NHC(O)O, NHC(O)NH, NHC(O)S, OC(O)NH, S(CO)NH, C(O)NH, and NHC(O);

R is selected from R_2, OR_2;

R_1 is selected from H, COW, SO_3^-, OR_3, =O, CN, NH_2, $NHCO(C_6\text{-}C_{10})Ar$, where Ar may possibly be substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen;

R_2 is selected from H, straight or branched C_1-C_4 alkyl, possibly substituted by at least one halogen;

R_3 is selected from H, straight or branched C_1-C_4 alkyl, possibly substituted by at least one halogen, $(C_6\text{-}C_{10})ArCH_2$, where Ar is possibly substituted by halogens, NO_2, OH, C_1-C_4 alkyl and alkoxy, said alkyl and alkoxy possibly substituted by at least one halogen;

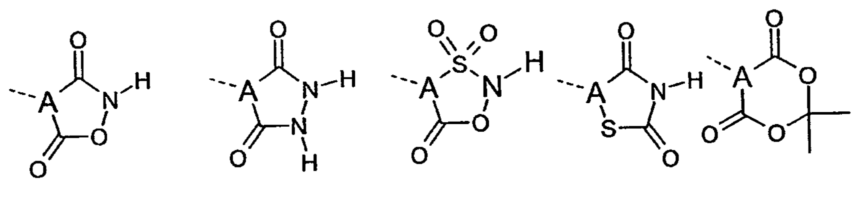
W is selected from OH, OR_4, NH_2;

R_4 is straight or branched C_1-C_4 alkyl;

Y is selected from OH, OR_5, NH_2;

R_5 is straight or branched C_1-C_4 alkyl;

or A, COY and R1 together form a cycle of the type:



their pharmacologically acceptable salts, racemic mixtures, individual enantiomers, geometric isomers or stereoisomers, and tautomers.

2. Compounds according to claim 1, in which Ar is a heteroaryl, preferably containing nitrogen as the heteroatom, and preferably f is 0, m is 1 or 2, Q is oxygen, and R is hydrogen.

3. Compounds according to claim 1, in which Ar is an aryl, possibly substituted by one or more halogen atoms, alkyl, alkoxy or lower haloalkyl, nitro, mono- or di-alkylamine, and preferably f is 0, m is 0, 1 or 2, Q is oxygen or HNC(O)O, and R is hydrogen.

4. Compounds according to one of claims 1-3, where R_1 is COW.

5. Compound according to claim 1, selected from the group consisting of:

i. Diethyl 4-[2-(1-indolyl)ethoxy]benzylidenemalonate;

ii. Diethyl 4-[2-(1-indolyl)ethoxy]benzylmalonate;

iii. Dimethyl 4-[2-(1-indolyl)ethoxy]benzylidenemalonate;

iv. Dimethyl 4-[2-(1-indolyl)ethoxy]benzylmalonate;

v. 4-[2-(1-indolyl)ethoxy]benzylmalonic acid;

vi. Methyl (2S)-amino-2-[4-[2-(1-indolyl)ethoxy]phenyl]-acetate;

vii. Methyl 4-[2-(1-indolyl)ethoxy]benzoate;

viii. Methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]propanoate;

ix. Methyl 2-[4-[2-(1-indolyl)ethoxy]phenyl]acetate;

x. Methyl 2-sulpho-2-[4-[2-(1-indolyl)ethoxy]phenyl]acetate sodium salt;

xi. Methyl (S)-2-benzoylamino-2-[4-[2-(1-indolyl)ethoxy]-phenyl]acetate;

xii. Methyl 2-hydroxy-3-[4-[2-(1-indolyl)ethoxy]phenyl]-propanoate;

xiii. Dimethyl 4-[2-[4-(dimethylamino)phenyl]ethoxy]benzylmalonate;

xiv. Methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyano-propenoate;

xv. Methyl 3-[4-[2-(1-indolyl)ethoxy]phenyl]-2-cyano-propanoate;

xvi. Dimethyl 4-[2-(3-indolyl)ethoxy]benzylidenemalonate;

xvii. Dimethyl 4-[2-(1-naphthyl)ethoxy]benzylmalonate;

xviii. Dimethyl 4-[2-(2-pyridyl)ethoxy]benzylmalonate;

xix. Dimethyl 4-[2-(4-chlorophenyl)ethoxy]benzylmalonate;

xx. 5-[4-[2-(4-chlorophenyl)ethoxy]phenylmethylene]-thiazolidine-2,4-dione;

xxi. 5-[4-[2-(4-chlorophenyl)ethoxy]phenylmethyl]thiazolidine-2,4-dione;

xxii. Dimethyl 3-[2-(4-chlorophenyl)ethoxy]benzylmalonate;

xxiii. Dimethyl 3-[2-(phenyl)ethoxy]benzylmalonate;

xxiv. Dimethyl 3-[N-(4-trifluoromethylbenzyl)carbamoyl]-4-methoxybenzylmalonate;

xxv. Dimethyl 4-methoxy-3-[2-(4-chlorophenyl)ethoxy]benzylmalonate:

xxvi. Dimethyl 3-(2-phenylethoxy)-4-methoxy benzylmalonate;

xxvii. Dimethyl 4-[2-(4-methoxyphenyl)ethoxy]benzylmalonate;

xxviii. Dimethyl 4-[3-(4-methoxyphenyl)propyloxy]benzyl-malonate;

xxix. Dimethyl 4-[2-(2-naphthyl)ethoxy]benzylmalonate;

xxx. (2S)-2-benzoylamino-3-[4-[(4-methoxybenzyl)-carbamoyl-]oxyphenyl]ethyl propanoate;

xxxi. Dimethyl 4-[[(4-methoxybenzyl)carbamoyl]oxy]benzyl-malonate;

xxxii. Dimethyl 4-[[(4-trifluorotolyl)carbamoyl]oxy]benzyl-malonate;

xxxiii. Dimethyl 4-[[(2,4-dichlorophenyl)carbamoyl]oxy]benzyl-malonate;

xxxiv. Dimethyl 4-[[(4-chlorophenyl)carbamoyl]oxy]benzyl-malonate;

xxxv. Dimethyl 4-[2-(pyridinio)ethoxy]benzylmalonate methane-sulphonate;

xxxvi. Dimethyl 4-[[(4-nitrophenyl)carbamoyl]oxy]benzyl-malonate;

xxxvii. Dimethyl 3-[[(4-methoxybenzyl)carbamoyl]oxy]benzyl-malonate;

xxxviii. Dimethyl 3-[[(4-butylphenyl)carbamoyl]oxy]benzyl-malonate;

xxxix. Dimethyl 4-[[(4-butylphenyl)carbamoyl]oxy]benzyl-malonate;

xl. Dimethyl 3-[[(4-chlorophenyl)carbamoyl]oxy]benzyl-malonate;

xli. (Z)-2-ethoxy-3-[4-[2-(4-chloro-phenyl)ethoxy]-phenyl] ethyl propenoate;

xlii. (E)-2-ethoxy-3-[4-[2-(4-chloro-phenyl)ethoxy]-phenyl]ethyl propenoate;

xliii. (R,S)-2-ethoxy-3-[4-[2-(phenyl)ethoxy]phenyl]ethyl propanoate;

xliv. (R,S)-2-ethoxy-3-[4-[2-(4-chloro-phenyl)ethoxy]-phenyl-]methyl propanoate;

xlv. Dimethyl 4-[2-(2,3-dimethyl-1-indolyl)ethoxy]benzyl-malonate.

6. Compounds according to claims 1-5 as medicines.

7. Pharmaceutical compositions containing at least one compound according to claims 1-5 in mixtures with pharmaceutically acceptable vehicles and/or excipients.

8. Use of the compounds according to claims 1-5 for the preparation of a medicine with serum glucose and serum lipid lowering activity.

9. Use of the compounds according to claims 1-5 for the preparation of a medicine for the prophylaxis and treatment of diabetes, particularly type 2, and its complications, Syndrome X, the various forms of insulin resistance and hyperlipdaemias.

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(71) Applicant (*for all designated States except US*): **SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.** [IT/IT]; Viale Shakespeare, 47, I-00144 Roma (IT).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **GIANNESSI, Fabio** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). **TASSONI, Emanuela** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km 30,400, I-00040 Pomezia (IT). **DELL'UOMO, Natalina** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km 30,400, I-00040 Pomezia (IT). **BRUNETTI, Tiziana** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT). **TINTI, Maria, Ornella** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Via Pontina, km 30,400, I-00040 Pomezia (IT). **ARDUINI, Arduino** [IT/IT]; c/o Sigma-Tau Industrie Farmaceutiche Riunite S.p., A., Via Pontina, Km.30,400, I-00040 Pomezia (IT). **PESSOTTO, Pompeo** [IT/IT]; c/o Sigma-Tau Industrie Faramceutiche Riunite S.p., A., Via Pontina, Km. 30, 400, I-00040 Pomezia (IT).

(74) Agents: **SPADARO, Marco** et al.; Cavattoni- Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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Published:
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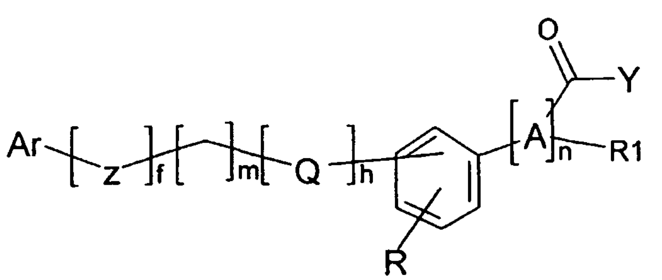
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 29 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENY(ALKYL)CARBOXYLIC ACID DERIVATIVES AND DIONIC PHENYLALKYLHETEROCYCLIC DERIVATIVES AND THEIR USE AS MEDICINES WITH SERUM GLUCOSE AND/OR SERUM LIPID LOWERING ACTIVITY



(I)

(57) Abstract: Formula (I) compounds are described: Where the groups are as defined here below, and their use as medinies, particularly as serum glucose and serum lipid lowering agents. Said medicines are useful for the prophylaxis and treatment of diabetes, particularly type 2, and its complications, Syndrome X, the various forms of insulin resistance, and hyperlipidaemias, and present reduced side effects, and, particularly, reduced or no liver toxicity.

WO 2003/059864 A3

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/08 C07D209/12 C07D213/30 C07D213/20 C07D277/20
C07D277/34 C07C69/734 C07C271/58 C07C271/48 C07C233/66
C07C235/60 C07C217/76 A61K31/427 A61K31/19 A61K31/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, CHEM ABS Data, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KITAJIMA, HIROSHI ET AL: "Preparation of 3-Aromatic-substituted propionic acid or acrylic acid derivatives as antidiabetics" retrieved from STN Database accession no. 134:41915 XP002262201 abstract and RNs 312689-52-4, 312690-33-8, 312690-69-0, 312690-71-4, 312690-73-6, 312689-53-5, 312690-29-2 & JP 2000 344748 A (WELLFIDE K. K., JAPAN) 12 December 2000 (2000-12-12) ---	1,8,9
X	WO 99 62871 A (ASTRA AB) 9 December 1999 (1999-12-09) examples 26b, 98-100; claims 1,38 ---	1,8,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2003	03/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHINKAI H ET AL: "ISOXAZOLIDINE-3,5-DIONE AND NONCYCLIC 1,3-DICARBONYL COMPOUNDS AS HYPOGLECEMIC AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 11, 1998, pages 1927-1933, XP002151949 ISSN: 0022-2623 table 1, compound 18 ---	1,8,9
X	EP 0 930 299 A (JAPAN TOBACCO INC) 21 July 1999 (1999-07-21) claims 1,4,7; examples 57,58 ---	1,8,9
X	US 5 306 726 A (HULIN BERNARD) 26 April 1994 (1994-04-26) column 1 (16-21) and column 27 (65-66) ---	1,8,9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 232 945 A (HULIN BERNARD) 3 August 1993 (1993-08-03) column 1 (9-22); column 24 (37-38)	1,8,9
X	WO 91 19702 A (PFIZER) 26 December 1991 (1991-12-26) page 54, lines 3-8, claims 1, 34	1,8,9
X	EP 0 008 203 A (TAKEDA CHEMICAL INDUSTRIES LTD) 20 February 1980 (1980-02-20) claims 1 and 7; examples 1212,13,16-24, 38-42, 13	1,8,9
X	EP 0 193 256 A (TAKEDA CHEMICAL INDUSTRIES LTD) 3 September 1986 (1986-09-03) claim 6	1,8,9
X	MOMOSE Y ET AL: "STUDIES ON ANTIDIABETIC AGENTS. X. SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PIOGLITAZONE AND RELATED COMPOUNDS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 39, no. 6, June 1991 (1991-06), pages 1440-1445, XP000986045 ISSN: 0009-2363 table II and Table III (Y=0) table II	1,8,9
X	EP 0 528 734 A (ADIR) 24 February 1993 (1993-02-24) examples 7,8,21,22,38	1,8,9
X	EP 0 676 398 A (SANKYO CO) 11 October 1995 (1995-10-11) claims 1,27; examples 3,4,6	1,8,9
X	EP 0 846 693 A (KYORIN SEIYAKU KK) 10 June 1998 (1998-06-10) examples 15-26,28,37,38; claims 1,14 claim 1; tables 1,14	1,8,9

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INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KINOSHITA, SUSUMU ET AL: "Preparation of N-benzyl(dioxothiazolidyl)benzamides and their use as oral antidiabetics and hypolipemic agents" retrieved from STN Database accession no. 128:13261 XP002262202 abstract and RNs 199167-85-6, -86-7, -87-8, -89-0, -81-2, -82-3, -83-4, -84-5 & JP 09 301963 A (KYORIN PHARMACEUTICAL CO., LTD., JAPAN) 25 November 1997 (1997-11-25) ---	1,8,9
X	EP 0 881 219 A (KYORIN SEIYAKU KK) 2 December 1998 (1998-12-02) claims 1,8; example 25 ---	1,8,9
X	SOHDA T ET AL: "STUDIES ON ANTIDIABETIC AGENTS. III. 5-ARYLTHIAZOLIDINE-2,4-DIONES AS POTENT ALDOSE REDUCTASE INHIBITORS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 30, no. 10, 1982, pages 3601-3616, XP002024094 ISSN: 0009-2363 table III, compounds 32-35 ---	1,8,9
X	EP 0 526 658 A (KYORIN SEIYAKU KK) 10 February 1993 (1993-02-10) claims 1,6; example 60 ---	1,8,9
X	CURTIS, NEIL R. ET AL: "Synthesis and SAR of diiodotyrosine-derived glycine-site N-methyl-D-aspartate receptor ligands" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (1996), 6(10), 1145-1150 , XP004134886 compound 18 ---	1,8
X	WO 01 40170 A (ASTRAZENECA AB) 7 June 2001 (2001-06-07) examples 11(a), 15(a), 21(a), 21(b) ---	1
X	WO 00 78312 A (MERCK) 28 December 2000 (2000-12-28) preparative examples 4, 61, 67 ---	1

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KITAJIMA, HIROSHI ET AL: "Hybridization of non-sulfonylurea insulin secretagogue and thiazolidinedione-derived insulin sensitizer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2000), 10(21), 2453-2456 , XP004224238 compound 12 (R=5-ethyl-2-pyridyl) ---	1
X	WO 94 19335 A (OTSUKA) 1 September 1994 (1994-09-01) page 90, line 10 -----	1

2

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4, 6-9 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 6-9 (in part)

Present claims 1-4 and 6-9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I, as disclosed in claim 5, where Ar is phenyl, naphthyl, 1-indolyl, 3-indolyl, 2 pyridyl, or pyridinium, all of them optionally substituted as indicated in claim 1 and 3; -'z!f'CH2!m'Q!h is -CH2-CH2-O, -CH2-CH2-CH2-O, -NH(C=O)O-, -CH2NH(C=O)O-, or -CH2NH(C=O)-; the phenylene moeity is a p-phenylene , a m-phenylene or a 2-CH3O-m-phenylene group, and the -'A!nR1C(=O)-Y group represents a thiazolidine-2,4-dione or a carboxylic acid or ester as defined in claim 1

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
JP 2000344748	A	12-12-2000	NONE			
WO 9962871	A	09-12-1999	AT	251130	T	15-10-2003
			AU	4667099	A	20-12-1999
			AU	752262	B2	12-09-2002
			AU	4667299	A	20-12-1999
			BR	9910913	A	06-03-2001
			BR	9910921	A	06-03-2001
			CA	2334107	A1	09-12-1999
			CA	2334374	A1	09-12-1999
			CN	1312795	T	12-09-2001
			CN	1311769	T	05-09-2001
			DE	69911770	D1	06-11-2003
			EE	200000717	A	15-08-2001
			EE	200000725	A	17-06-2002
			EP	1084101	A1	21-03-2001
			EP	1084102	A1	21-03-2001
			HU	0103226	A2	28-01-2002
			JP	2002516898	T	11-06-2002
			JP	2002516899	T	11-06-2002
			NO	20006114	A	02-02-2001
			NO	20006116	A	02-02-2001
			NZ	508453	A	30-06-2003
			PL	344681	A1	19-11-2001
			PL	344682	A1	19-11-2001
			WO	9962870	A1	09-12-1999
			WO	9962871	A1	09-12-1999
			SK	17672000	A3	06-08-2001
			SK	17692000	A3	10-05-2001
			TR	200003543	T2	20-04-2001
			TR	200003583	T2	21-05-2001
			TW	446694	B	21-07-2001
			US	6630600	B1	07-10-2003
			US	6362360	B1	26-03-2002
			ZA	200006771	A	20-05-2002
			ZA	200006773	A	20-02-2002
			AT	246674	T	15-08-2003
			AU	752261	B2	12-09-2002
			AU	4667199	A	20-12-1999
			BR	9910928	A	13-02-2001
			CA	2333938	A1	09-12-1999
			CN	1311772	T	05-09-2001
			DE	69910203	D1	11-09-2003
			EE	200000720	A	15-04-2002
			EP	1084103	A1	21-03-2001
			HR	20000782	A1	30-06-2001
			HU	0103376	A2	29-05-2002
EP 0930299	A	21-07-1999	JP	3215048	B2	02-10-2001
			JP	9323982	A	16-12-1997
			AU	740444	B2	01-11-2001
			AU	3866597	A	06-03-1998
			BG	103268	A	29-12-2000
			BR	9711627	A	24-08-1999
			EE	9900069	A	15-10-1999
			EP	0930299	A1	21-07-1999
			NO	990700	A	19-04-1999
			NZ	334738	A	26-01-2001

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0930299	A		PL	331861	A1	16-08-1999
			SK	21099	A3	16-05-2000
			US	6204277	B1	20-03-2001
			CN	1233241	A	27-10-1999
			CZ	9900536	A3	14-07-1999
			WO	9807699	A1	26-02-1998
US 5306726	A	26-04-1994	US	5089514	A	18-02-1992
			US	5438074	A	01-08-1995
			AT	149156	T	15-03-1997
			AU	646052	B2	03-02-1994
			AU	7995691	A	07-01-1992
			CA	2084898	A1	15-12-1991
			DE	69124798	D1	03-04-1997
			DE	69124798	T2	12-06-1997
			DK	533781	T3	07-07-1997
			EP	0533781	A1	31-03-1993
			ES	2098356	T3	01-05-1997
			FI	925640	A	11-12-1992
			GR	3022714	T3	30-06-1997
			HU	65603	A2	28-07-1994
			IE	912003	A1	18-12-1991
			IL	98447	A	31-12-1995
			JP	2581523	B2	12-02-1997
			JP	7149636	A	13-06-1995
			JP	7005513	B	25-01-1995
			JP	5507920	T	11-11-1993
			NO	924799	A	14-12-1992
			NZ	238528	A	27-07-1993
			PT	97950	A ,B	31-03-1992
			WO	9119702	A1	26-12-1991
			ZA	9104519	A	27-01-1993
US 5232945	A	03-08-1993	NONE			
WO 9119702	A	26-12-1991	US	5089514	A	18-02-1992
			AT	149156	T	15-03-1997
			AU	646052	B2	03-02-1994
			AU	7995691	A	07-01-1992
			CA	2084898	A1	15-12-1991
			DE	69124798	D1	03-04-1997
			DE	69124798	T2	12-06-1997
			DK	533781	T3	07-07-1997
			EP	0533781	A1	31-03-1993
			ES	2098356	T3	01-05-1997
			FI	925640	A	11-12-1992
			GR	3022714	T3	30-06-1997
			HU	65603	A2	28-07-1994
			IE	912003	A1	18-12-1991
			IL	98447	A	31-12-1995
			JP	2581523	B2	12-02-1997
			JP	7149636	A	13-06-1995
			JP	7005513	B	25-01-1995
			JP	5507920	T	11-11-1993
			NO	924799	A	14-12-1992
			NZ	238528	A	27-07-1993
			PT	97950	A ,B	31-03-1992
			WO	9119702	A1	26-12-1991

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9119702	A		US	5438074 A	01-08-1995
			US	5306726 A	26-04-1994
			ZA	9104519 A	27-01-1993
EP 0008203	A	20-02-1980	JP	1433701 C	07-04-1988
			JP	55022636 A	18-02-1980
			JP	62042903 B	10-09-1987
			CA	1131644 A1	14-09-1982
			DE	2963585 D1	21-10-1982
			DK	325079 A ,B,	05-02-1980
			EP	0008203 A1	20-02-1980
			ES	8102107 A1	01-04-1981
			US	4287200 A	01-09-1981
			US	4340605 A	20-07-1982
			US	4438141 A	20-03-1984
			US	4444779 A	24-04-1984
EP 0193256	A	03-09-1986	AT	41931 T	15-04-1989
			AU	572719 B2	12-05-1988
			BR	1100325 A3	27-06-2000
			CA	1277323 C	04-12-1990
			CS	9104079 A3	15-04-1992
			DE	3662689 D1	11-05-1989
			DK	21986 A	20-07-1986
			DK	171614 B1	24-02-1997
			EP	0193256 A1	03-09-1986
			ES	8705886 A1	01-08-1987
			FI	860232 A ,B,	20-07-1986
			GR	860124 A1	19-05-1986
			HK	3692 A	17-01-1992
			HU	41775 A2	28-05-1987
			IE	58928 B1	01-12-1993
			JP	1853588 C	07-07-1994
			JP	5066956 B	22-09-1993
			JP	61267580 A	27-11-1986
			KR	9210046 B1	13-11-1992
			LU	90719 A9	26-03-2001
			LV	5779 A4	20-12-1996
			MX	9202933 A1	30-06-1992
			NO	860141 A ,B,	21-07-1986
			PT	81859 A ,B	01-02-1986
			SG	105691 G	14-02-1992
			US	4687777 A	18-08-1987
			ZA	8600203 A	30-09-1987
EP 0528734	A	24-02-1993	FR	2680512 A1	26-02-1993
			AT	144503 T	15-11-1996
			AU	645709 B2	20-01-1994
			AU	2110892 A	25-02-1993
			CA	2076444 A1	21-02-1993
			DE	69214755 D1	28-11-1996
			DE	69214755 T2	07-05-1997
			DK	528734 T3	07-04-1997
			EP	0528734 A1	24-02-1993
			ES	2095432 T3	16-02-1997
			GR	3022116 T3	31-03-1997
			JP	1998886 C	08-12-1995
			JP	5213913 A	24-08-1993

INTERNATIONAL SEARCH REPORT

PCT/IT 03/0000/

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0528734	A		JP	7030055	B	05-04-1995
			NZ	244021	A	27-01-1995
			US	5330999	A	19-07-1994
			US	5296605	A	22-03-1994
			US	5266582	A	30-11-1993
			ZA	9206276	A	02-03-1993
EP 0676398	A	11-10-1995	AT	222895	T	15-09-2002
			AT	207488	T	15-11-2001
			AU	683348	B2	06-11-1997
			AU	1638395	A	19-10-1995
			AU	700354	B2	07-01-1999
			AU	3244397	A	23-10-1997
			AU	712294	B2	04-11-1999
			AU	8709398	A	03-12-1998
			CA	2146701	A1	12-10-1995
			CN	1118781	A ,B	20-03-1996
			CZ	9500910	A3	17-12-1997
			DE	69523358	D1	29-11-2001
			DE	69523358	T2	11-07-2002
			DE	69528000	D1	02-10-2002
			DE	69528000	T2	28-05-2003
			DK	1022274	T3	28-10-2002
			DK	676398	T3	10-12-2001
			EP	1022274	A1	26-07-2000
			EP	0676398	A2	11-10-1995
			ES	2180477	T3	16-02-2003
			ES	2165895	T3	01-04-2002
			FI	951731	A	12-10-1995
			HK	1029338	A1	03-01-2003
			HK	1011365	A1	16-08-2002
			HU	73765	A2	30-09-1996
			HU	72627	A2	28-05-1996
			IL	113313	A	22-09-1999
			IL	115269	A	20-06-1999
			JP	7330728	A	19-12-1995
			NO	951398	A	12-10-1995
			NO	983900	A	12-10-1995
			NZ	270917	A	20-12-1996
			PT	1022274	T	29-11-2002
			PT	676398	T	28-03-2002
			RU	2114844	C1	10-07-1998
			RU	2151145	C1	20-06-2000
			TW	407156	B	01-10-2000
			TW	503237	B	21-09-2002
			US	5962470	A	05-10-1999
			US	5977365	A	02-11-1999
			US	6117893	A	12-09-2000
			US	5624935	A	29-04-1997
			US	5834501	A	10-11-1998
			US	5739345	A	14-04-1998
			ZA	9502990	A	21-12-1995
EP 0846693	A	10-06-1998	JP	3144624	B2	12-03-2001
			JP	9048771	A	18-02-1997
			AT	212341	T	15-02-2002
			AU	698896	B2	12-11-1998
			AU	5844696	A	18-12-1996

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0846693	A		CA	2220698	A1	05-12-1996
			DE	69618792	D1	14-03-2002
			DE	69618792	T2	10-10-2002
			DK	846693	T3	06-05-2002
			EP	0846693	A1	10-06-1998
			US	6001862	A	14-12-1999
			US	6147101	A	14-11-2000
			US	6030990	A	29-02-2000
			CA	2417403	A1	05-12-1996
			CA	2417408	A1	05-12-1996
			CN	1336366	A	20-02-2002
			CN	1186489	A ,B	01-07-1998
			ES	2170858	T3	16-08-2002
			HU	9802565	A2	28-04-1999
			WO	9638428	A1	05-12-1996
			JP	2001139565	A	22-05-2001
			PT	846693	T	31-05-2002
			TW	400328	B	01-08-2000
JP 9301963	A	25-11-1997	NONE			
EP 0881219	A	02-12-1998	JP	9169746	A	30-06-1997
			AU	705538	B2	27-05-1999
			AU	2011697	A	14-07-1997
			EP	0881219	A1	02-12-1998
			US	5948803	A	07-09-1999
			CA	2239245	A1	26-06-1997
			CN	1205695	A ,B	20-01-1999
			HU	0000449	A2	28-02-2001
			WO	9722600	A1	26-06-1997
EP 0526658	A	10-02-1993	JP	3053490	B2	19-06-2000
			JP	5092960	A	16-04-1993
			CA	2081113	A1	26-08-1992
			DE	69227080	D1	29-10-1998
			DE	69227080	T2	20-05-1999
			DK	526658	T3	14-06-1999
			EP	0526658	A1	10-02-1993
			KR	9612206	B1	16-09-1996
			US	5342850	A	30-08-1994
			AT	171448	T	15-10-1998
			AU	645886	B2	27-01-1994
			AU	1205992	A	15-09-1992
			ES	2122991	T3	01-01-1999
			HU	66972	A2	30-01-1995
			WO	9214719	A1	03-09-1992
WO 0140170	A	07-06-2001	AU	766547	B2	16-10-2003
			AU	2240101	A	12-06-2001
			BR	0016133	A	20-08-2002
			CA	2392035	A1	07-06-2001
			CN	1433401	T	30-07-2003
			EP	1237857	A1	11-09-2002
			JP	2003515581	T	07-05-2003
			NO	20022603	A	10-07-2002
			WO	0140170	A1	07-06-2001
			US	2003018207	A1	23-01-2003

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00007

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0078312	A	28-12-2000	AU	5875500	A	09-01-2001
			CA	2376919	A1	28-12-2000
			EP	1194146	A1	10-04-2002
			JP	2003502369	T	21-01-2003
			WO	0078312	A1	28-12-2000
			US	6399640	B1	04-06-2002
WO 9419335	A	01-09-1994	AT	212018	T	15-02-2002
			AU	669427	B2	06-06-1996
			AU	6045894	A	14-09-1994
			CA	2134347	A1	27-08-1994
			CN	1106982	A ,B	16-08-1995
			CN	1184105	A ,B	10-06-1998
			DE	69429641	D1	21-02-2002
			DE	69429641	T2	29-08-2002
			DK	638075	T3	18-02-2002
			EP	0638075	A1	15-02-1995
			ES	2168294	T3	16-06-2002
			JP	2821661	B2	05-11-1998
			JP	7133264	A	23-05-1995
			WO	9419335	A1	01-09-1994
			JP	10167965	A	23-06-1998
			KR	257180	B1	15-05-2000
			KR	250701	B1	01-07-2000
			PT	638075	T	28-06-2002
			US	5677322	A	14-10-1997